

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problems Mailbox.**

THIS PAGE BLANK (USPTO)

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 265/36, 279/16, A61K 31/535, 31/54	A1	(11) International Publication Number: WO 99/50257 (43) International Publication Date: 7 October 1999 (07.10.99)
(21) International Application Number: PCT/US98/26708 (22) International Filing Date: 15 December 1998 (15.12.98) (30) Priority Data: 60/080,142 31 March 1998 (31.03.98) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BERRYMAN, Kent, Alan [US/US]; P.O. Box 2494, Silverthorne, CO 80498 (US). DOWNING, Dennis, Michael [US/US]; 3737 Burbank, Ann Arbor, MI 48105 (US). DUDLEY, Danette, Andrea [US/US]; 290 Village Green Boulevard #201, Ann Arbor, MI 48105 (US). EDMUNDS, Jeremy, John [GB/US]; 3957 Beech Drive, Ypsilanti, MI 48197 (US). NARASIMHAN, Lakshmi, Sourirajan [IN/US]; 45680 Larchmont Drive, Canton, MI 48197 (US). RAPUNDALO, Stephen, Taras [CA/US]; 3106 Bluett Road, Ann Arbor, MI 48105 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: BENZOXAZINONES/BENZOTHIAZINONES AS SERINE PROTEASE INHIBITORS		
(57) Abstract This invention discloses benzoxazinone and benzothiazinone compounds which display inhibitory effects on serine proteases such as factor Xa, thrombin, and/or factor VIIa. The invention also discloses pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable compositions comprising the compounds or their salts, and methods of using them as therapeutic agents for treating or preventing disease states in mammals characterized by abnormal thrombosis.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

-1-

BENZOXAZINONES/BENZOTHIAZINONES AS SERINE PROTEASE INHIBITORS

FIELD OF THE INVENTION

In one aspect, this invention discloses benzoxazinone and benzothiazinone
5 compounds which display inhibitory effects on serine proteases such as factor Xa,
thrombin, and/or factor VIIa. The invention also discloses pharmaceutically
acceptable salts of the compounds, pharmaceutically acceptable compositions
comprising the compounds or their salts, and methods of using them as
therapeutic agents for treating or preventing disease states in mammals
10 characterized by abnormal thrombosis.

BACKGROUND OF THE INVENTION

In economically developed countries, cardiovascular disease still
represents a major cause of mortality. In particular, abnormal coagulation and
inappropriate thrombus formation within blood vessels precipitates many acute
15 cardiovascular disease states. While it has long been recognized that a variety of
plasma proteins such as fibrinogen, serine proteases, and cellular receptors are
involved in hemostasis, it is the abnormal regulation that has emerged as
important contributing factors to cardiovascular disease. Thrombin can be
considered the key or principal regulatory enzyme in the coagulation cascade; it
20 serves a pluralistic role as both a positive and negative feedback regulator in
normal hemostasis. However, in some pathologic conditions, the former is
amplified through catalytic activation of cofactors required for thrombin
generation such as factor Xa. Factor Xa, as part of the prothrombinase complex
composed of nonenzymatic cofactor Va, calcium ions, and a phospholipid
25 membrane surface regulates the generation of thrombin from its zymogen
prothrombin. Furthermore, the location of the prothrombinase complex at the
convergence of both the intrinsic and extrinsic coagulation pathways suggests that

-2-

inhibition of factor Xa, and hence thrombin generation, may be a viable approach to limiting the procoagulant activity of thrombin.

Indeed, ample evidence exists for the role of factor Xa inhibitors as anticoagulants. Antistasin, a potent inhibitor of blood coagulation factor Xa from the Mexican leech: *Haementeria officinalis*, displays antithrombotic activity in various models of arterial and venous thrombosis (Lapatto et al., *Embo. J.*, 1997:5151-5161). Other protein or polypeptide factor Xa inhibitors include recombinant tick anticoagulant peptide (rTAP), which is known to accelerate the recombinant tissue plasminogen activator mediated clot lysis and prevent acute reocclusion in the dog, hence indicating factor Xa inhibitors may be useful as an adjunct to thrombolytic therapy (Mellott et al., *Fibrinolysis*, 1993:195-202). Furthermore, in a canine coronary artery electrolytic lesion model, rTAP was demonstrated to reduce thrombus mass and time to occlusion in the absence of dramatic hemodynamic or hemostatic changes indicating the primary role for factor Xa in the process of arterial thrombosis (Lynch et al., *Thromb. Haemostasis*, 1995:640-645; Schaffer et al., *Circulation*, 1991:1741-1748). On the venous side, rTAP was also demonstrated to reduce fibrin deposition in a rabbit model of venous thrombosis while having little affect on systemic hemostatic parameters (Fioravanti et al., *Thromb. Res.*, 1993:317-324). In addition to these relatively high molecular weight proteins that are not suitable as oral antithrombotic agents, there also exist examples of low molecular weight factor Xa inhibitors. In particular Dx9065a, a low molecular weight synthetic factor Xa inhibitor, has also shown antithrombotic potential in various experimental thrombosis rat models. In both arteriovenous shunt and venous stasis models, inhibition of thrombus formation was achieved at doses that had little effect on APTT, indicating that DX9065a is effective in preventing thrombosis and hence has therapeutic antithrombotic potential (Wong et al., *Thromb. Res.*, 1996:117-126).

The majority of factor Xa inhibitors known to date have been previously summarized in two reviews (Edmunds et al., *Annual Reports in Medicinal Chemistry*, 1996:51 and Kunitada and Nagahara, *Curr. Pharm. Des.*, 1996:531-542). However, it is readily apparent that there still exists a need for more effective agents that regulate factor Xa proteolytic activity.

-3-

Some benzoxazinones and benzothiazinones have been reported and these compounds have displayed marked pharmacological activity:

Moriyama et al., *Biol. Pharm. Bull.*, 1997:701-703;

Gezginci et al., *Farmaco*, 1997:255-256;

5 Sastry et al., *Indian J. Chem., Sect. B*, 1989:882-884;

United States Patent 680718;

Bornschein et al., *Pharmazie*, 1977:695-697 and Pfeifer et al., *Pharmazie*, 1977:587-592;

Japanese Application 60166674;

10 European Application 116368;

Japanese Application 01272524;

United States Patent 4,786,635;

Fujita M. et al., *J. Med. Chem.*, 1990:1898;

Japanese Application 03118380;

15 Japanese Application 09227561;

Shridhar et al., *Indian J. Chem., Sect. B*, 1985;24B(12):1263-1267;

Bornschein et al., *Pharmazie*, 1977;32(11):695-697 and 1977;32(10):587-592;

Thuillier et al., *Eur. J. Med. Chem. - Chim. Ther.*, 1975;10(1):37-42;

20 German Patent 2044530; and

United States Patent 3401166.

None of the above articles set forth above, however, disclose or suggest compounds set forth herein that are inhibitors of serine proteases involved in the blood coagulation cascade.

25

SUMMARY OF THE INVENTION

One object of the present invention is to provide serine protease inhibitors that display inhibitory activity towards enzymes involved in the coagulation cascade and principally the target enzymes, factor Xa, thrombin, and factor VIIa.

-4-

A further object of the present invention is to provide serine protease inhibitors that display inhibitory activity towards the target enzyme factor Xa and are provided for in a pharmacologically acceptable state.

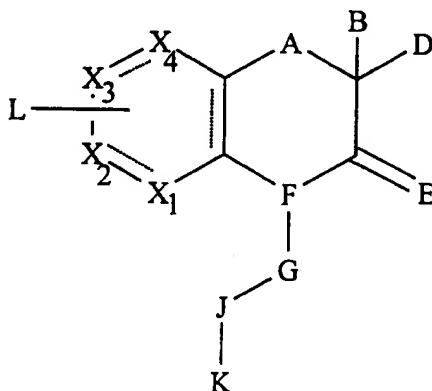
5 Still a further object of the present invention is to provide for the use of these factor Xa inhibitors and formulations thereof as anticoagulant and factor Xa inhibitory agents.

Yet a further object of the present invention is to provide for the use of these factor Xa inhibitors and formulations thereof for therapeutic treatment of various thrombotic maladies.

10 A further object of the present invention is a process for the synthesis of these low molecular weight thrombin inhibitors. The enzyme inhibitors of the present invention are encompassed by the structure of general Formula 1 set forth below.

15 The present invention meets these objectives and provides for novel compounds that display antithrombotic activity. More specifically, the present invention provides for novel compounds that display antithrombotic activity via the inhibition of factor Xa as reflected in Formula 1, or pharmaceutically acceptable salts or prodrug forms thereof. The present invention also provides pharmaceutically acceptable compositions comprising the novel compounds or
20 their salts or prodrug forms, and methods of using them as therapeutic agents for treating or preventing disease states in mammals characterized by abnormal thrombosis.

Thus in a first embodiment, the present invention provides novel compounds of Formula 1:



1

-5-

or stereoisomers or pharmaceutically acceptable salt forms or prodrugs thereof, wherein:

A is selected from O, S, S(=O), S(=O)(=O), OCH₂, CH₂O, SCH₂, S(=O)CH₂, S(=O)(=O)CH₂, CH₂S, CH₂S(=O), CH₂S(=O)(=O);

5 B is selected from hydrogen, cycloalkyl, heteroalkyl, cycloalkylalkyl, heteroalkylalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, each optionally substituted with R₁ and R₂;

D is selected from H, (C₃₋₂₀)alkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heteroalkylalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, each
10 optionally substituted with R₁ and R₂;

E is absent or selected from O, S, NH;

F is selected from N, NCH₂, CH₂N;

G is absent or selected from alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl, cycloalkyl interrupted by one or more heteroatoms;

15 J is absent or selected from aryl or heterocycle each optionally substituted with R₁ and R₂;

K is absent or selected from an alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl interrupted by one or more heteroatoms, cycloalkylalkyl interrupted by one or more heteroatoms, each optionally
20 substituted with R₁ and R₂;

L is selected from H, chlorine, fluorine, bromine, iodine, OH, O(alkyl), amine, alkyl, fluoroalkyl, amide, NO₂, SH, S(O)_n(alkyl), SO₃H, SO₃alkyl, nitrile aldehyde, ketone, acid, ester, urea, Oalkylamide, Oalkylester, Oalkylacid, Nalkylacid, alkylamine, alkylamide, alkylketone, alkylacid, alkylester,
25 alkylurea, Nalkylamide, Nalkylester, NC(=O)alkyl, NC(=O)aryl, NC(=O)cycloalkyl, NC(=O)cycloalkylalkyl, NC(=O) alkylaryl, R₁, R₂;

R₁ is selected from H, amine, alkylamine, amide, C(=NH)NHNH₂, alkylC(=NH)NHNH₂, C(=NH)NHOH, alkylC(=NH)NHOH, NHC(=NH)NH₂, alkylNHC(=NH)NH₂, C(=S)NH₂, alkylC(=S)NH₂,

-6-

$C(=NH)alkyl$, $alkylC(=NH)alkyl$, $C(=NR_3)N(R_4)(R_5)$,
 $alkylC(=NR_3)N(R_4)(R_5)$;

R_2 is selected from H, chlorine, fluorine, bromine, iodine, OH, Oalkyl, amine,

alkylaldehyde, alkylamide, alkylester, alkylketone, alkylacid,

5 Oalkylamide, Oalkylacid, Oalkylester, aninealkylacid, aminealkylamide,
 aminealkylester, $NC(=O)alkyl$, $NC(=O)aryl$, $NC(=O)cycloalkyl$,

$NC(=O)alkylaryl$, alkylamine, amide, aldehyde, ester, ketone, NO_2 , SH,

$S(O)_n(C_{1-10}alkyl)$, SO_3H , SO_3alkyl , CHO, acid, alkyl, $C(=NH)alkyl$,

$C(=NH)NHNH_2$, $alkylC(=NH)NHNH_2$, $C(=NH)NHOH$,

10 $alkylC(=NH)NHOH$, $NHC(=NH)NH_2$, $alkylNHC(=NH)NH_2$, $C(=S)NH_2$,

$alkylC(=S)NH_2$, $alkylC(=NH)alkyl$, $C(=NR_3)N(R_4)(R_5)$,

$alkylC(=NR_3)N(R_4)(R_5)$;

R_3 , R_4 , and R_5 are a hydrogen atom, alkyl group having 1 to 4 carbon atoms

optionally interrupted by a heteroatom, or R_4 and R_5 are bonded to form

15 $-(CH_2)_p-W-(CH_2)_q-$, wherein p and q are an integer of 2 or 3, a certain

position on the methylene chain is unsubstituted or substituted by an alkyl

group having 1 to 4 carbon atoms, W is a direct bond, $-CH_2-$, $-O-$,

$-N(R_6)-$, or $-S(O)_r-$ wherein R_6 is H or alkyl, and r is 0 or 1 or 2;

n is selected from 0, 1, 2;

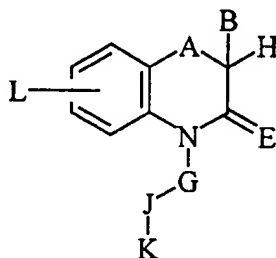
20 X_1 is C or N;

X_2 is C or N;

X_3 is C or N; and

X_4 is C or N.

Preferred compounds according to this invention have the Formula 2:



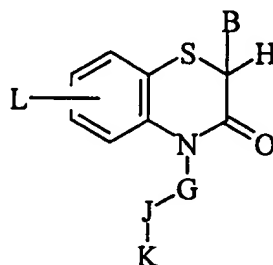
25

2

-7-

or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein A, B, E, G, J, K, and L are defined as above.

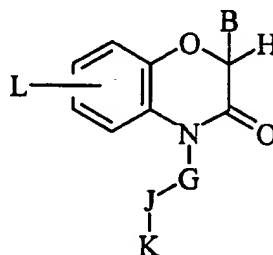
Another preferred group of compounds have the Formula 3:



3

5 or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein B, G, J, K, and L are defined as above.

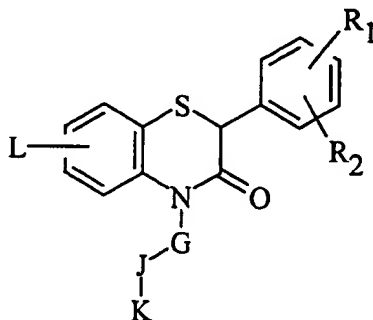
Another preferred group of compounds have the Formula 4:



4

10 or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein B, G, J, K, and L are defined as above.

Even more preferred compounds have the Formula 5:

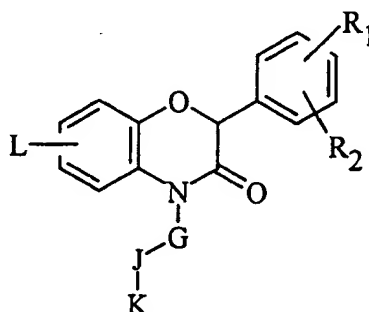


5

-8-

or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein R_1 , R_2 , G , J , K , and L are as defined above.

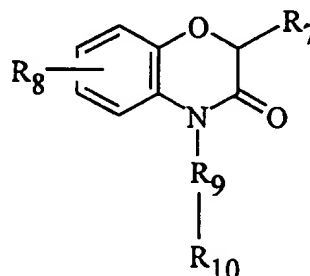
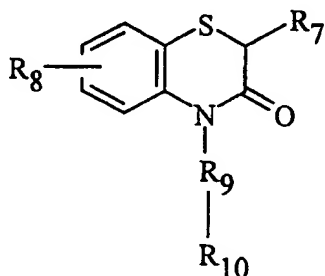
Another more preferred group of compounds have the Formula 6:



6

5 or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein R_1 , R_2 , G , J , K , and L are as defined above.

The most preferred compounds provided by this invention are compounds of Formulas 7 and 8:



7,8

10 or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein

R_7 is (3-amidino)phenyl, (3-hydroxy)phenyl, [3-hydroxylamino(imino)methyl]-phenyl, [3-hydrazino(imino)methyl]-phenyl, (3-aminomethyl)phenyl, (3-amino)phenyl, (3-methylamino)phenyl, (3-dimethylamino)phenyl, (5-amidino-2-hydroxy)phenyl, (1-amidino)piperid-3-yl, (5-amidino-2-methoxy)phenyl, (1-amidino)pyrrolid-3-yl, (5-amidino)thien-2-yl, (5-amidino)furan-2-yl, (5-amidino)-1,3-oxazol-2-yl, (2-amidino)-1,3-oxazol-5-yl, 1H-pyrazol-5-yl, tetrahydro-1H-pyrazol-3-yl, (1-amidino)tetrahydro-1H-pyrazol-3-yl, (2-amidino)-1H-imidazol-4-yl, (2-amino)-1H-imidazol-4-yl, (5-amidino)-1H-imidazol-2-yl, (5-amino)-1H-imidazol-2-yl, pyridin-3-yl, (4-amino)pyridin-3-yl,

20

-9-

(4-dimethylamino)pyridin-3-yl, (6-amino)pyridin-2-yl,
 (6-amidino)pyridin-2-yl, (2-amino)pyridin-4-yl, (2-amidino)pyridin-4-yl,
 (2-amidino)pyrimidin-4-yl, (2-amino)pyrimidin-4-yl, (4-amidino)pyrimidin-
 2-yl, (4-amino)pyrimidin-2-yl, (6-amidino)pyrazin-2-yl, (6-amino)pyrazin-
 2-yl, (4-amidino)-1,3,5-triazin-2-yl, (4-amino)-1,3,5-triazin-2-yl,
 (3-amidino)-1,2,4-triazin-5-yl, (3-amino)-1,2,4-triazin-5-yl,
 (3-amidino)benzyl, (3-amino)benzyl, (3-aminomethyl)benzyl,
 (1-amidino)piperid-3-ylmethyl, (1-amidino)pyrrolid-3-ylmethyl,
 (5-amidino)thien-2-ylmethyl, (5-amidino)furan-2-ylmethyl,
 (5-amidino)oxazol-2-ylmethyl, (2-amidino)imidazol-5-ylmethyl,
 (5-amidino)imidazol-2-ylmethyl, (6-amidino)pyridin-2-ylmethyl,
 (6-amino)pyridin-2-ylmethyl, (2-amidino)pyrimidin-4-ylmethyl,
 (2-amino)pyrimidin-4-ylmethyl, (4-amidino)pyrimidin-2-ylmethyl,
 (4-amino)pyrimidin-2-ylmethyl, (6-amidino)pyrazin-2-ylmethyl,
 (6-amino)pyrazin-2-ylmethyl, 3-aminocyclohexyl, 3-amidinocyclohexyl,
 3-aminocyclohexylmethyl, 3-amidinocyclohexylmethyl,
 3-aminocyclopentyl, 3-amidinocyclopentyl, 3-aminocyclopentylmethyl,
 and 3-amidinocyclopentylmethyl;

R₈ is Br, I, C₂H₅, H, Cl, F, SH, SMe, CF₃, CH₃, CO₂H, CO₂Me, CN,
 C(=NH)NH₂, C(=NH)NHOH, C(=NH)NHNH₂, C(=O)NH₂, CH₂OH,
 CH₂NH₂, NO₂, OH, OMe, OCH₂Ph, OCH₂CO₂H, O(CH₂)₂CO₂H,
 O(CH₂)₃CO₂H, NHCH₂CO₂H, NH(CH₂)₂CO₂H, NH(CH₂)₃CO₂H,
 OCH₂CH₂OH, OCH₂(1H-tetrazol-5-yl), NH₂, NHButyl, NMe₂, NHPh,
 NHCH₂Ph, NHC(=O)Me, NHC(=O)c-Hexyl, NHC(=O)CH₂c-Hexyl,
 NHC(=O)Ph, NHC(=O)CH₂Ph, NHS(=O)₂Me, NHS(=O)₂c-Hexyl,
 NHS(=O)₂CH₂c-Hexyl, NHS(=O)₂Ph, and NHS(=O)₂CH₂Ph;

R₉ is (CH₂)₅, (CH₂)₄, (CH₂)₆, CH₂C(=O)NHCH₂CH₂,
 CH₂CH₂NHC(=O)CH₂, (CH₂)₂NH(CH₂)₂, (CH₂)₂O(CH₂)₂, C₆H₄,
 CH₂C₆H₄, C₆H₄CH₂, C₆H₁₀, CH₂C₆H₁₀, C₆H₁₀CH₂, C₅H₈,
 CH₂C₅H₈, C₅H₈CH₂, and CH₂CH=CHCH₂CH₂; and

-10-

R₁₀ is piperidinyl, 2,6-dimethylpiperidinyl, 2,2,6,6-tetramethyl-piperidinyl-4-one, 2,2,6,6-tetramethyl piperidinyl, (2-carboxy)piperidinyl, (3-carboxy)piperidinyl, (4-carboxy)piperidinyl, 3,5-dimethylpiperidinyl, (4-hydroxy)piperidinyl, (2-imino)piperidinyl, piperidin-4-one-yl, (2-dimethylaminomethyl)-piperidinyl, (4-dimethylamino)-piperidinyl, (4-sulphonyloxy)-piperidinyl, (2-phenyl)piperidinyl, 2,5-dimethylpyrrolidinyl, pyrrolidinyl, (2-carboxy)pyrrolidinyl, (3-N-acetyl-N-methyl)pyrrolidinyl, (3-amino)pyrrolidinyl, (2,5-bis-methoxymethyl)-pyrrolidinyl, 2-hydroxymethyl-pyrrolidinyl, 2-hydroxymethyl-5-methyl-pyrrolidinyl, diisopropylamino, diethylamino, methylamino, 1-methyl-4,5-dihydro-1H-imidazol-2-yl, 2,5-dimethyl-1H-1-imidazolyl, morpholinyl, 2,6-dimethylmorpholinyl, piperazinyl, 2,6-dimethylpiperazinyl, 1H-pyrazolyl, tetrahydro-1H-pyrazolyl, and 2,5-dimethyltetrahydro-1H-1-pyrazolyl.

In one embodiment of Formulas 7 and 8, R₈, R₉, and R₁₀ are as above and R₇ is (2-hydroxy, 5-amidino)phenyl. In another embodiment of Formulas 7 and 8, R₇, R₉, and R₁₀ are as above and R₈ is H. In another embodiment of Formulas 7 and 8, R₇, R₈, and R₁₀ are as above and R₉ is (CH₂)₅. In another embodiment of Formulas 7 and 8, R₇, R₈, and R₁₀ is 2,6-dimethylpiperidinyl. in another embodiment of Formulas 7 and 8, R₇ is as defined above and R₈ is H, R₉ is (CH₂)₅ and R₁₀ is 2,6-dimethylpiperidinyl. In another embodiment of Formulas 7 and 8, R₇ is as defined above and R₈ is H, R₉ is (CH₂)₅ and R₁₀ is 2,5-dimethylpyrrolidinyl.

Representative compounds of the present invention include:

3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-4-methoxybenzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(3-hydroxyphenyl)-2*H*-1,4-benzothiazin-3(4*H*)-one;

- 11 -

- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-*N*-hydroxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-*N*-hydroxybenzenecarboximidamide;
- 5 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidohydrazide;
- 2-[3-(Aminomethyl)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-(3-Aminophenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 10 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-[3-(methylamino)phenyl]-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-[3-(Dimethylamino)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 15 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-4-hydroxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)tetrahydro-1(2*H*)-pyridinecarboximidamide;
- 20 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-pyrrolidinecarboximidamide;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-thiophenecarboximidamide;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-furancarboximidamide;
- 25 2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,3-oxazole-5-carboximidamide;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,3-oxazole-2-carboximidamide;
- 30 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(1*H*-pyrazol-5-yl)-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-pyrazolidinecarboximidamide;

-12-

- 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1*H*-imidazole-2-carboximidamide;
2-(2-Amino-1*H*-imidazol-4-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 5 2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1*H*-imidazole-5-carboximidamide;
2-(5-Amino-1*H*-imidazol-2-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 10 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(3-pyridinyl)-2*H*-1,4-benzothiazin-3(4*H*)-one;
2-(4-Amino-3-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
2-[4-(Dimethylamino)-3-pyridinyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 15 2-(6-Amino-2-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
6-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyridinecarboximidamide;
2-(2-Amino-4-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 20 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyridinecarboximidamide;
4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyrimidinecarboximidamide;
- 25 2-(2-Amino-4-pyrimidinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-4-pyrimidinecarboximidamide;
2-(4-Amino-2-pyrimidinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 30 6-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyrazinecarboximidamide;

-13-

2-(6-Amino-2-pyrazinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,3,5-triazine-2-carboximidamide;

5 2-(4-Amino-1,3,5-triazin-2-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,2,4-triazine-3-carboximidamide;

10 2-(3-Amino-1,2,4-triazin-5-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]benzenecarboximidamide;

2-(3-Aminobenzyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

15 2-[3-(Aminomethyl)benzyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]tetrahydro-1(2*H*)-pyridinecarboximidamide;

20 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1-pyrrolidinecarboximidamide;

5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-thiophenecarboximidamide;

25 5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-furancarboximidamide;

2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1,3-oxazole-5-carboximidamide;

5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1*H*-imidazole-2-carboximidamide;

30 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1*H*-imidazole-5-carboximidamide;

6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyridinecarboximidamide;

-14-

- 2-[(6-Amino-2-pyridinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 4-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyrimidinecarboximidamide;
- 5 2-[(2-Amino-4-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-4-pyrimidinecarboximidamide;
- 2-[(4-Amino-2-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 10 6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyrazinecarboximidamide;
- 2-[(6-Amino-2-pyrazinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 15 2-(3-Aminocyclohexyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)cyclohexanecarboximidamide;
- 2-[(3-Aminocyclohexyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 20 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]cyclohexanecarboximidamide;
- 2-(3-Aminocyclopentyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 25 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)cyclopentanecarboximidamide;
- 2-[(3-Aminocyclopentyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]cyclopentanecarboximidamide;
- 30 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

-15-

3-(4-6-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]hexyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

2-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)-*N*-2-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]ethylacetamide;

3-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)-*N*-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]methylpropanamide;

3-4-[2-(2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethylamino)ethyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-[4-(2-2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethoxyethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]phenyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylphenyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylcyclohexyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-(4-3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclopentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-[4-(3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclopentylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

-16-

3-[4-(3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylcyclopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

5 3-(4-(*E*)-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]-2-pentenyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-[3-Oxo-4-(5-piperidinopentyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-3-Oxo-4-[5-(2,2,6,6-tetramethylpiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

10 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-2-piperidinecarboxylic acid;

1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-3-piperidinecarboxylic acid;

15 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-4-piperidinecarboxylic acid;

3-4-[5-(3,5-Dimethylpiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-4-[5-(4-Hydroxypiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

20 3-4-[5-(2-Iminopiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-3-Oxo-4-[5-(4-oxopiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

25 3-[4-(5-2-[(Dimethylamino)methyl]piperidinopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-(4-5-[4-(Dimethylamino)piperidino]pentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-4-piperidinesulfonic acid;

30 3-3-Oxo-4-[5-(2-phenylpiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-4-[5-(2,5-Dimethyl-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

-17-

3-3-Oxo-4-[5-(1-pyrrolidinyl)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-2-pyrrolidinecarboxylic acid;

5 *N*-1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]tetrahydro-1*H*-pyrrol-3-yl-*N*-methylacetamide;

3-4-[5-(3-Amino-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

10 3-(4-5-[2,5-Bis(methoxymethyl)-1-pyrrolidinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(4-5-[2-(Hydroxymethyl)-1-pyrrolidinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(4-5-[2-(Hydroxymethyl)-5-methyl-1-pyrrolidinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

15 3-4-[5-(Diisopropylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-4-[5-(Diethylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

20 3-4-[5-(Methylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-4-[5-(1-Methyl-1*H*-imidazol-2-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-4-[5-(2,5-Dimethyl-1*H*-imidazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

25 3-[4-(5-Morpholinopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-4-[5-(3,5-Dimethylmorpholino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

30 3-[3-Oxo-4-(5-piperazinopentyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-4-[5-(2,6-Dimethylpiperazino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

-18-

3-3-Oxo-4-[5-(1*H*-pyrazol-1-yl)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-[3-Oxo-4-(5-tetrahydro-1*H*-pyrazol-1-yl)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

5 3-4-[5-(2,5-Dimethyltetrahydro-1*H*-pyrazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

3-(6-Chloro-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

10 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-fluoro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-sulfanyl-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

15 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(methylsulfanyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

20 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid;

25 Methyl 2-3-[amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate;

3-(6-Cyano-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

30 2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboximidamide;

-19-

2-3-[amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-*N*-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboximidamide;

3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-
5 [hydrazino(imino)methyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide;

3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-
10 (hydroxymethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-(6-(Aminomethyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-methoxy-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(6-(Benzyloxy)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)oxy]acetic acid;

3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)oxy]propanoic acid;

4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)oxy]butanoic acid;

-20-

2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)amino]acetic acid;

5 3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)amino]propanoic acid;

4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)amino]butanoic acid;

10 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(2-hydroxyethoxy)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

15 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-(2*H*-1,2,3,4-tetraazol-5-ylmethoxy)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

3-(6-Amino-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

20 3-(6-(Butylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(6-(Dimethylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

25 3-(6-Anilino-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(6-(Benzylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

30 *N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)acetamide;

-21-

N-(2-3-[Amino(imino)methyl]phenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)cyclohexanecarboxamide;

5 *N*-(2-3-[Amino(imino)methyl]phenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)-2-cyclohexylacetamide;

N-(2-3-[Amino(imino)methyl]phenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)benzenecarboxamide;

10 *N*-(2-3-[Amino(imino)methyl]phenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)-2-phenylacetamide;

15 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-[(methylsulfonyl)amino]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(6-[(Cyclohexylsulfonyl)amino]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

20 3-(6-[(Cyclohexylmethyl)sulfonyl]amino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-[(phenylsulfonyl)amino]-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

25 3-(6-[(Benzylsulfonyl)amino]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-methoxybenzenecarboximidamide;

30 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(3-hydroxyphenyl)-2*H*-1,4-benzoxazin-3(4*H*)-one;

-22-

- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-hydroxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidohydrazide;
- 5 2-[3-(Aminomethyl)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 2-(3-Aminophenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-[3-(methylamino)phenyl]-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 10 2-[3-(Dimethylamino)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide;
- 15 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)tetrahydro-1(2*H*)-pyridinecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-pyrrolidinecarboximidamide;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-2-thiophenecarboximidamide;
- 20 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-2-furancarboximidamide;
- 2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1,3-oxazole-5-carboximidamide;
- 25 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1,3-oxazole-2-carboximidamide;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(1*H*-pyrazol-5-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-tetrahydro-1*H*-pyrazol-3-yl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 30 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-pyrazolidinecarboximidamide;

-23-

- 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1*H*-imidazole-2-carboximidamide;
2-(2-Amino-1*H*-imidazol-4-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 5 2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1*H*-imidazole-5-carboximidamide;
2-(5-Amino-1*H*-imidazol-2-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 10 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(3-pyridinyl)-2*H*-1,4-benzoxazin-3(4*H*)-one;
2-(4-Amino-3-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
2-[4-(Dimethylamino)-3-pyridinyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 15 2-(6-Amino-2-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
6-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-2-pyridinecarboximidamide;
2-(2-Amino-4-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 20 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-2-pyridinecarboximidamide;
4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-2-pyrimidinecarboximidamide;
- 25 2-(2-Amino-4-pyrimidinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-pyrimidinecarboximidamide;
- 30 2-(4-Amino-2-pyrimidinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
6-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-2-pyrazinecarboximidamide;

-24-

- 2-(6-Amino-2-pyrazinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1,3,5-triazine-2-carboximidamide;
- 5 2-(4-Amino-1,3,5-triazin-2-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1,2,4-triazine-3-carboximidamide;
- 2-(3-Amino-1,2,4-triazin-5-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 10 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]benzenecarboximidamide;
- 2-(3-Aminobenzyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 15 2-[3-(Aminomethyl)benzyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]tetrahydro-1(2*H*)-pyridinecarboximidamide;
- 20 3-[(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-1-pyrrolidinecarboximidamide;
- 5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-2-thiophenecarboximidamide;
- 5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-2-furancarboximidamide;
- 25 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-1,3-oxazole-5-carboximidamide;
- 5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-1*H*-imidazole-2-carboximidamide;
- 30 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-1*H*-imidazole-5-carboximidamide;
- 6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-2-pyridinecarboximidamide;

-25-

2-[(6-Amino-2-pyridinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

4-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-2-pyrimidinecarboximidamide;

5 2-[(2-Amino-4-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-4-pyrimidinecarboximidamide;

10 2-[(4-Amino-2-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-2-pyrazinecarboximidamide;

2-[(6-Amino-2-pyrazinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

15 2-(3-Aminocyclohexyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)cyclohexanecarboximidamide;

20 2-[(3-Aminocyclohexyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]cyclohexanecarboximidamide;

2-(3-Aminocyclopentyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

25 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)cyclopentanecarboximidamide;

2-[(3-Aminocyclopentyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

30 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]cyclopentanecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

-26-

3-(4-6-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]hexyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

2-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-*N*-2-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]ethylacetamide;

3-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-*N*-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]methylpropanamide;

3-4-[2-(2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethylamino)ethyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-[4-(2-2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethoxyethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]phenyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylphenyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylcyclohexyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-(4-3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclopentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-[4-(3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclopentylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

-27-

3-[4-(3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylcyclopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

5 3-(4-(*E*)-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]-2-pentenyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-[3-Oxo-4-(5-piperidinopentyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-3-Oxo-4-[5-(2,2,6,6-tetramethylpiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

10 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)pentyl]-2-piperidinecarboxylic acid;

1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)pentyl]-3-piperidinecarboxylic acid;

15 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)pentyl]-4-piperidinecarboxylic acid;

3-4-[5-(3,5-Dimethylpiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-4-[5-(4-Hydroxypiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

20 3-4-[5-(2-Iminopiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-3-Oxo-4-[5-(4-oxopiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

25 3-[4-(5-2-[(Dimethylamino)methyl]piperidinopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-(4-5-[4-(Dimethylamino)piperidino]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)pentyl]-4-piperidinesulfonic acid;

30 3-3-Oxo-4-[5-(2-phenylpiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-4-[5-(2,5-Dimethyl-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

-28-

3-3-Oxo-4-[5-(1-pyrrolidinyl)pentyl]-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)pentyl]-2-pyrrolidinecarboxylic acid;

5 *N*-1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)pentyl]tetrahydro-1*H*-pyrrol-3-yl-*N*-methylacetamide;

3-4-[5-(3-Amino-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

10 3-(4-5-[2,5-Bis(methoxymethyl)-1-pyrrolidinyl]pentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(4-5-[2-(Hydroxymethyl)-1-pyrrolidinyl]pentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(4-5-[2-(Hydroxymethyl)-5-methyl-1-pyrrolidinyl]pentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

15 3-4-[5-(Diisopropylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-4-[5-(Diethylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

20 3-4-[5-(Methylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-4-[5-(1-Methyl-1*H*-imidazol-2-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-4-[5-(2,5-Dimethyl-1*H*-imidazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

25 3-[4-(5-Morpholinopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-4-[5-(3,5-Dimethylmorpholino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

30 3-[3-Oxo-4-(5-piperazinopentyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-4-[5-(2,6-Dimethylpiperazino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

-29-

3-3-Oxo-4-[5-(1*H*-pyrazol-1-yl)pentyl]-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-[3-Oxo-4-(5-tetrahydro-1*H*-pyrazol-1-yl)pentyl]-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

5 3-4-[5-(2,5-Dimethyltetrahydro-1*H*-pyrazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-(6-Chloro-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

10 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-fluoro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-sulfanyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

15 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(methylsulfanyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

20 2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylic acid;

Methyl 2-3-[amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate;

25 3-(6-Cyano-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboximidamide;

30 2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-*N*-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboximidamide;

-30-

3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-[hydrazino(imino)methyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

5 2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxamide;

3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(hydroxymethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

10 3-(6-(Aminomethyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

15 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-methoxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

20 3-(6-(Benzyloxy)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)oxy]acetic acid

25 3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)oxy]propanoic acid;

4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)oxy]butanoic acid;

30 2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)amino]acetic acid;

-31-

3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)amino]propanoic acid;

5 4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)amino]butanoic acid;

3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(2-hydroxyethoxy)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

10 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-(2*H*-1,2,3,4-tetraazol-5-ylmethoxy)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarboximidamide;

3-(6-Amino-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

15 3-(6-(Butylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

20 3-(6-(Dimethylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(6-Anilino-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

25 3-(6-(Benzylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)acetamide;

30 *N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)cyclohexanecarboxamide;

-32-

N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-2-cyclohexylacetamide;

5 *N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)benzenecarboxamide;

N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-2-phenylacetamide;

10 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-[(methylsulfonyl)amino]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-(6-[(Cyclohexylsulfonyl)amino]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

3-(6-[(Cyclohexylmethyl)sulfonyl]amino-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

20 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-[(phenylsulfonyl)amino]-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylbenzenecarboximidamide;

3-(6-[(Benzylsulfonyl)amino]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;

25 2*H*-1,4-Benzoxazin-3(4*H*)-one, 4-[3-(2,6-dimethyl-1-piperidinyl)propyl]-2-phenyl-;

4-[5-(2,5-Dimethyl-pyrrolidin-1-yl)-pentyl]-2-phenyl-4*H*-benzo[1,4]oxazin-3-one;

30 2*H*-1,4-Benzoxazin-3(4*H*)-one, 4-[5-[bis(1-methylethyl)amino]pentyl]-2-phenyl-;

2*H*-1,4-Benzoxazin-3(4*H*)-one, 4-[3-(2,5-dimethyl-1-pyrrolidinyl)propyl]-2-phenyl-;

-33-

- 2*H*-1,4-Benzoxazin-3(4*H*)-one, 4-[3-[bis(1-methylethyl)amino]propyl]-2-phenyl-;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-phenyl-4*H*-benzo[1,4]oxazin-3-one;
- 5 4-(5-Diethylamino-pentyl)-2-phenyl-4*H*-benzo[1,4]oxazin-3-one;
- 2-Phenyl-4-(5-pyrrolidin-1-yl-pentyl)-4*H*-benzo[1,4]oxazin-3-one;
- 2-[5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentyl]-isoindole-1,3-dione;
- 4-(5-Imidazol-1-yl-pentyl)-2-phenyl-4*H*-benzo[1,4]oxazin-3-one;
- 10 2-(4-Chloro-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4*H*-benzo[1,4]oxazin-3-one;
- 2-(2-Chloro-phenyl)-4-[5-(2,5-dimethyl-pyrrolidin-1-yl)-pentyl]-4*H*-benzo[1,4]oxazin-3-one;
- 2-(2-Chloro-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4*H*-benzo[1,4]oxazin-3-one;
- 15 5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentanamidine;
- 2-Phenyl-4-(5-piperidin-1-yl-pentyl)-4*H*-benzo[1,4]oxazin-3-one;
- 2-(4-Chloro-phenyl)-4-[5-(2,5-dimethyl-pyrrolidin-1-yl)-pentyl]-4*H*-benzo[1,4]oxazin-3-one;
- 20 2-Phenyl-4-(5-pyrrolidin-1-yl-pentyl)-4*H*-benzo[1,4]oxazin-3-one;
- compound with trifluoro-acetic acid;
- 3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzonitrile;
- 25 4-[6-(2,5-Dimethyl-pyrrolidin-1-yl)-hexyl]-2-phenyl-4*H*-benzo[1,4]oxazin-3-one;
- 3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzamidine;
- 2-Naphthalen-2-yl-4-(5-piperidin-1-yl-pentyl)-4*H*-benzo[1,4]oxazin-3-one;
- 30 4-(5-Amino-pentyl)-2-phenyl-4*H*-benzo[1,4]oxazin-3-one;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-phenyl-4*H*-benzo[1,4]oxazin-3-one;

-34-

- 6-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 7-Methoxy-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 5 8-Chloro-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 3-Oxo-2-phenyl-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbonitrile;
- 4-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzamidine;
- 10 1-[5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentyl]-piperidine-2,6-dione;
- 3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionitrile;
- 15 4-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyronitrile;
- 5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentanenitrile;
- N-[3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propyl]-guanidine;
- 20 N-[5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentyl]-guanidine;
- 4-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzamidine;
- 25 2-(4-Methoxy-phenyl)-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 7-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 5-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 30 6-Methoxy-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;

-35-

N-Hydroxy-4-(3-oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzamidine;

6-Chloro-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;

5 2-(4-Methoxy-phenyl)-4-(5-piperazin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;

2-(4-Hydroxy-phenyl)-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;

10 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-hydroxy-phenyl)-4H-benzo[1,4]oxazin-3-one;

2-(4-Methoxy-phenyl)-4-[5-(4-methyl-piperazin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzonitrile;

15 4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-thiobenzamide;

20 [2-(4-Methoxy-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetic acid;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-N-hydroxy-benzamidine;

Benzenecarboximidic acid, 4-[3,4-dihydro-4-[5-(2,6-dimethyl-1-piperidiny)pentyl]-3-oxo-2H-1,4-benzoxazin-2-yl]-, hydrazide;

25 6-Amino-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;

4-(5-Bromo-pentyl)-2-(3,4-dimethoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;

30 4-(5-Bromo-pentyl)-2-(3,4,5-trimethoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;

4-(5-Bromo-pentyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;

-36-

- N-[2-(2,6-Dimethyl-piperidin-1-yl)-ethyl]-2-[2-(4-methoxy-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetamide;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(3,4,5-trimethoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 5 2-(3,4-Dimethoxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 2-(4-Bromo-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 8-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 10 2-(4-Benzylamino-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 2-(4-Methoxy-phenyl)-4-[5-(2,2,6,6-tetramethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 15 4-(2-Bromo-ethyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 4-(5-Bromo-pentyl)-2-(3,4-dichloro-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 4-(2-Hydroxy-ethyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 20 2-(3,4-Dichloro-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 4-[3-(2,6-Dimethyl-piperidin-1-ylmethyl)-benzyl]-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 25 4-(2-Amino-ethyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 2-(2,6-Dimethyl-piperidin-1-yl)-N-{2-[2-(4-methoxy-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-5-oxo-pentyl]-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 30 3-{4-[4-(2,6-Dimethyl-piperidin-1-yl)-butyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

-37-

3-{4-[6-(2,6-Dimethyl-piperidin-1-yl)-hexyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

2-(5-Aminomethyl-2-hydroxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;

5 2-(3-Aminomethyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-7-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

10 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-methoxy-benzamidine;

2-(5-Aminomethyl-2-methoxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-N-hydroxy-4-methoxy-benzamidine;

15 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-N-hydroxy-benzamidine;

3-{7-Chloro-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

4-(5-Bromo-pentyl)-2-phenyl-4H-benzo[1,4]oxazin-3-one;

20 3-[3-Oxo-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;

N-{2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl}-acetamide;

25 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-hydroxy-benzamidine;

3-[4-(5-Diisopropylamino-pentyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;

3-(4-{4-[(Diisopropylamino)-methyl]-benzyl}-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-benzamidine;

30 3-{4-[4-(2,6-Dimethyl-piperidin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-hydroxy-benzamidine;

-38-

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-N-methyl-benzamidine;

{2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl}-acetic acid;

5 3-(4-{3-[(Diisopropylamino)-methyl]-benzyl}-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-benzamidine;

3-{4-[3-(2,6-Dimethyl-piperidin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

10 2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid;

3-{3-Oxo-4-[4-(pyridin-2-ylamino)-butyl]-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

15 2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid methyl ester;

3-[4-(5-Dihexylamino-pentyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;

3-{4-[4-(Methyl-pyridin-2-yl-amino)-butyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

20 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-[3-(imino-morpholin-4-yl-methyl)-phenyl]-4H-benzo[1,4]oxazin-3-one;

3-{3-Oxo-4-[4-(pyrimidin-2-ylamino)-butyl]-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

25 3-[4-(4-Cyclohexylamino-butyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;

3-{4-[5-(2,5-Dimethyl-pyrrolidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

3-[4-(5-Morpholin-4-yl-pentyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;

30 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-2,3-dihydroxy-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

4-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-N,N-dimethyl-benzamide;

-39-

- 2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxylic acid;
- 3-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-N,N-dimethyl-benzamide;
- 5 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pent-2-enyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 3-[4-(5-Amino-pentyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;
- 10 2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxylic acid methyl ester;
- 4-Methoxy-3-[4-(4-methoxy-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzonitrile;
- 15 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pent-3-enyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 4-[2-(3-Cyano-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-N,N-dimethyl-benzamide;
- 3-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-5-(2,6-dimethyl-piperidin-1-ylmethyl)-benzoic acid;
- 20 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-hydroxy-benzamidine;
- 3-Acetyl-2-(2-methoxy-phenyl)-thiazolidine-4-carboxylic acid 4-cyano-2-{4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-phenyl ester;
- 25 3-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-5-(2,6-dimethyl-piperidin-1-ylmethyl)-N-hydroxy-benzamide;
- 4-(2-Dimethylamino-ethyl)-7-nitro-2-phenyl-4H-benzo[1,4]thiazin-3-one;
- 30 4-(2-Diethylamino-ethyl)-7-nitro-2-phenyl-4H-benzo[1,4]thiazin-3-one;

2*H*-1,4-Benzothiazin-3(4*H*)-one, 4-[2-(dimethylamino)ethyl]-7-nitro-2-phenyl-, monohydrochloride;

2*H*-1,4-Benzothiazin-3(4*H*)-one, 4-[2-(diethylamino)ethyl]-7-nitro-2-phenyl-, monohydrochloride;

5 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-methoxy-phenyl)-4*H*-benzo[1,4]thiazin-3-one;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-benzonitrile;

10 4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-thiobenzamide;

4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-methoxy-phenyl)-4*H*-benzo[1,4]thiazin-3-one; compound with trifluoro-acetic acid;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-benzonitrile;

15 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-benzamide;

4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(3-methoxy-phenyl)-2-(4-methoxy-phenyl)-4*H*-benzo[1,4]thiazin-3-one;

20 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-methoxy-phenyl)-1,1-dioxo-1,4-dihydro-2*H*-1,4-benzo[1,4]thiazin-3-one;

2-(4-Benzyloxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4*H*-benzo[1,4]thiazin-3-one;

2-(4-Butoxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4*H*-benzo[1,4]thiazin-3-one;

25 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-thiobenzamide;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-benzamidine;

30 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-*N*-hydroxy-benzamidine;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-2-yl}-benzamidine;

-41-

- 3-{4-[5-(2-Hydroxymethyl-pyrrolidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-benzamidine;
- 4-Allyl-2,2-diphenyl-4H-benzo[1,4]thiazin-3-one;
- 4-(2-Diethylamino-ethyl)-7-nitro-2-phenyl-4H-benzo[1,4]thiazin-3-one;
- 2-(3-Diethylamino-propylamino)-4-methyl-2-phenyl-4H-benzo[1,4]thiazin-3-one;
- 4-(2-Diethylamino-ethyl)-2,2-diphenyl-4H-benzo[1,4]thiazin-3-one;
- 2-Benzyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 2-Cyclohexyl-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]thiazin-3-one;
- 2H-1,4-Benzothiazin-3(4H)-one, 4-methyl-2,2-diphenyl-;
- 4-Ethyl-2-phenyl-2-piperidin-1-yl-4H-benzo[1,4]thiazin-3-one;
- 4-Methyl-2-phenyl-2-piperidin-1-yl-4H-benzo[1,4]thiazin-3-one;
- 3-{4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-piperidine-1-carboxamidine;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-piperidin-3-yl-4H-benzo[1,4]oxazin-3-one;
- 3-Oxo-2-phenyl-2,4-bis-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbonitrile;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-pyridin-2-yl-4H-benzo[1,4]oxazin-3-one;
- N-Hydroxy-3-oxo-2-phenyl-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxamidine;
- 3-Oxo-2-phenyl-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxamidine;
- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-thiobenzamide;
- 3-{4-[5-(Adamantan-1-ylamino)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 2-(3-Diethylamino-propylamino)-4-methyl-2-phenyl-4H-benzo[1,4]oxazin-3-one;

-42-

4-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-2-phenyl-2H/-1,4-benzoxazin-3(4H)-one; and
4-Methyl-2-phenyl-2H/-1,4-benzoxazin-3(4H)-one.

DETAILED DESCRIPTION OF THE INVENTION

5 The term "alkyl" means a straight, branched, saturated or unsaturated carbon chain having from 1 to 20 carbon atoms. Typical alkyl groups include methyl, isobutyl, pentyl, 2-methyl-pentyl, pent-1,4-dienyl, but-1-enyl and the like.

 The term "cycloalkyl" means a saturated or unsaturated carbon chain which forms a ring having from 3 to 20 carbon atoms. Typical examples include
10 cyclopropyl, cyclohexyl and the like.

 The term "cycloalkylalkyl" means a cycloalkyl group attached to an alkyl group wherein "cycloalkyl" and "alkyl" are as defined above and includes, for example, cyclopropylmethyl, cyclopentylethyl and the like.

 The term "heteroalkyl" means a straight, branched, saturated or
15 unsaturated carbon chain having from 1 to 20 carbon atoms wherein one or more carbon atoms is replaced by a heteroatom selected from oxygen, nitrogen, sulfur, sulphoxide or sulphone. Typical "heteroalkyl" groups include methoxymethyl, 3-thiomethylpropyl, and 2-thiomethoxyethoxymethyl and the like.

 The term "aryl" represents an unsaturated carbocyclic ring(s) of 6 to
20 16 carbon atoms which is optionally substituted with, OH, O(alkyl), SH, S(alkyl), amine, halogen, acid, ester, amide, alkyl ketone, aldehyde, nitrile, fluoroalkyl, amidine, nitro, sulphone, sulfoxide or (C₁₋₆)alkyl, thioamide, Oalkylaryl, benzylamino, C(NH)(NHNH₂), N-hydroxyamidine, N-methylamidine. Typical rings include phenyl, naphthyl, phenanthryl, and anthracenyl. Preferred aryl rings
25 are phenyl, substituted phenyl, and naphthyl.

 The term "arylalkyl" means an aromatic radical attached to an alkyl radical wherein "aryl" and "alkyl" are as defined above and includes, for example, benzyl, and naphthylmethyl.

 The term "heterocycle" means a saturated or unsaturated mono- or
30 polycyclic (i.e. bicyclic) ring incorporating one or more (i.e. 1-4) heteroatoms

-43-

selected from N, O, and S. It is understood that a heterocycle is optionally substituted with OH, O(alkyl), SH, S(alkyl), amine, halogen, acid, ester, amide, amidine alkyl ketone, aldehyde, nitrile, fluoroalkyl, nitro, sulphone, sulfoxide or C₁₋₆ alkyl. Examples of suitable monocyclic heterocycles include, but are not limited to substituted or unsubstituted thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, piperidinyl, pyrrolidinyl, piperazinyl, azetidiny, aziridinyl, morpholinyl, thietanyl, oxetanyl. Preferred monocydic heterocycles include, but are not limited to, 2- or 3- thienyl, 2- or 3-furanyl, 1-, 2-, or 3-pyrrolyl, 1-, 2-, 4-, or 5-imidazolyl, 1-, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 1, 3-, or 5-triazolyl, 1-, 2-, or 3-tetrazolyl, 2, 3-, or 4-pyridinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 1-, 2-, 3-, or 4- piperidinyl, 1-, 2-, or 3-pyrrolidinyl, 1- or 2-piperazinyl, 1-, 2-, or 3-azetidiny, 1- or 2-aziridinyl, 2-, 3-, or 4-morpholinyl, 2- or 3- thietanyl, 2- or 3-oxetanyl. Examples of suitable bicyclic heterocycles include, but are not limited to, indolizinyl, isoindolyl, benzothienyl, benzoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, and preferably 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 1-, 2-, 3-, 5-, 6-, 7-, or 8-indolizinyl, 1-, 2-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzothienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 1-, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl.

The term "heteroatom" as used herein represents oxygen, nitrogen, or sulfur (O, N, or S) as well as sulfoxyl or sulfonyl (SO or SO₂) unless otherwise indicated. It is understood that alkyl chains interrupted by one or more heteroatoms means that a carbon atom of the chain is replaced with a heteroatom having the appropriate valency. Preferably, an alkyl chain is interrupted by 1 to 4 heteroatoms and that two adjacent carbon atoms are not both replaced. Examples of such groups include methoxymethyl, 3-thiomethylpropyl, and 2-thiomethoxyethoxymethyl.

The term "amine" refers to a group such as NH₂, NHalkyl, NH(cycloalkyl), NH(cycloalkylalkyl), NH(aryl), NH(arylalkyl), NH(heteroaryl), NH(heteroarylalkyl), N(alkyl)(alkyl), N(alkyl)(cycloalkyl),

-44-

N(alkyl)(cycloalkylalkyl), N(alkyl)(aryl), N(alkyl)(arylalkyl),
 N(alkyl)(heteroaryl), N(alkyl)(heteroarylalkyl), N(cycloalkyl)(cycloalkyl),
 N(cycloalkyl)(cycloalkylalkyl), N(cycloalkyl)(aryl), N(cycloalkyl)(arylalkyl),
 N(cycloalkyl)(heteroaryl), N(cycloalkyl)(heteroarylalkyl),
 5 N(cycloalkylalkyl)(cycloalkylalkyl), N(cycloalkylalkyl)(aryl),
 N(cycloalkylalkyl)(arylalkyl), N(cycloalkylalkyl)(heteroaryl),
 N(cycloalkylalkyl)(heteroarylalkyl), N(aryl)(cycloalkylalkyl), N(aryl)(aryl),
 N(aryl)(arylalkyl), N(aryl)(heteroaryl), N(aryl)(heteroarylalkyl),
 N(arylalkyl)(arylalkyl), N(arylalkyl)(heteroaryl), N(arylalkyl)(heteroarylalkyl),
 10 N(heteroaryl)(heteroaryl), N(heteroaryl)(heteroarylalkyl),
 N(heteroarylalkyl)(heteroarylalkyl).

The term "acid" refers to $C(=O)OH$.

The term "ketone" refers to $C(=O)alkyl$, $C(=O)cycloalkyl$,
 $C(=O)cycloalkylalkyl$, $C(=O)aryl$, $C(=O)arylalkyl$, $C(=O)heteroaryl$,
 15 $C(=O)heteroarylalkyl$.

The term "ester" refers to a group such as $C(=O)Oalkyl$,
 $C(=O)Ocycloalkyl$, $C(=O)Ocycloalkylalkyl$, $C(=O)Oaryl$, $C(=O)Oarylalkyl$,
 $C(=O)Oheteroaryl$, $C(=O)Oheteroarylalkyl$.

The term "amide" refers to a group such as, $C(=O)NH_2$, $C(=O)NHalkyl$,
 20 $C(=O)NH(cycloalkyl)$, $C(=O)NH(cycloalkylalkyl)$, $C(=O)NH(aryl)$,
 $C(=O)NH(arylalkyl)$, $C(=O)NH(heteroaryl)$, $C(=O)NH(heteroarylalkyl)$,
 $C(=O)N(alkyl)(alkyl)$, $C(=O)N(alkyl)(cycloalkyl)$,
 $C(=O)N(alkyl)(cycloalkylalkyl)$, $C(=O)N(alkyl)(aryl)$, $C(=O)N(alkyl)(arylalkyl)$,
 $C(=O)N(alkyl)(heteroaryl)$, $C(=O)N(alkyl)(heteroarylalkyl)$,
 25 $C(=O)N(cycloalkyl)(cycloalkyl)$, $C(=O)N(cycloalkyl)(cycloalkylalkyl)$,
 $C(=O)N(cycloalkyl)(aryl)$, $C(=O)N(cycloalkyl)(arylalkyl)$,
 $C(=O)N(cycloalkyl)(heteroaryl)$, $C(=O)N(cycloalkyl)(heteroarylalkyl)$,
 $C(=O)N(cycloalkylalkyl)(cycloalkylalkyl)$, $C(=O)N(cycloalkylalkyl)(aryl)$,
 $C(=O)N(cycloalkylalkyl)(arylalkyl)$, $C(=O)N(cycloalkylalkyl)(heteroaryl)$,
 30 $C(=O)N(cycloalkylalkyl)(heteroarylalkyl)$, $C(=O)N(aryl)(cycloalkylalkyl)$,
 $C(=O)N(aryl)(aryl)$, $C(=O)N(aryl)(arylalkyl)$, $C(=O)N(aryl)(heteroaryl)$,
 $C(=O)N(aryl)(heteroarylalkyl)$, $C(=O)N(arylalkyl)(arylalkyl)$,

-45-

C(=O)N(arylalkyl)(heteroaryl), C(=O)N(arylalkyl)(heteroarylalkyl),
 C(=O)N(heteroaryl)(heteroaryl), C(=O)N(heteroaryl)(heteroarylalkyl),
 C(=O)N(heteroarylalkyl)(heteroarylalkyl).

The term "urea" refers to a group such as NHC(=O)N(alkyl)(alkyl),
 5 NHC(=O)N(alkyl)(cycloalkyl), NHC(=O)N(alkyl)(cycloalkylalkyl),
 NHC(=O)N(alkyl)(aryl), NHC(=O)N(alkyl)(arylalkyl),
 NHC(=O)N(alkyl)(heteroaryl), NHC(=O)N(alkyl)(heteroarylalkyl),
 NHC(=O)N(cycloalkyl)(cycloalkyl), NHC(=O)N(cycloalkyl)(cycloalkylalkyl),
 NHC(=O)N(cycloalkyl)(aryl), NHC(=O)N(cycloalkyl)(arylalkyl),
 10 NHC(=O)N(cycloalkyl)(heteroaryl), NHC(=O)N(cycloalkyl)(heteroarylalkyl),
 NHC(=O)N(cycloalkylalkyl)(cycloalkylalkyl), NHC(=O)N(cycloalkylalkyl)(aryl),
 NHC(=O)N(cycloalkylalkyl)(arylalkyl), NHC(=O)N(cycloalkylalkyl)(heteroaryl),
 NHC(=O)N(cycloalkylalkyl)(heteroarylalkyl), NHC(=O)N(aryl)(cycloalkylalkyl),
 NHC(=O)N(aryl)(aryl), NHC(=O)N(aryl)(arylalkyl),
 15 NHC(=O)N(aryl)(heteroaryl), NHC(=O)N(aryl)(heteroarylalkyl),
 NHC(=O)N(arylalkyl)(arylalkyl), NHC(=O)N(arylalkyl)(heteroaryl),
 NHC(=O)N(arylalkyl)(heteroarylalkyl), NHC(=O)N(heteroaryl)(heteroaryl),
 NHC(=O)N(heteroaryl)(heteroarylalkyl),
 NHC(=O)N(heteroarylalkyl)(heteroarylalkyl).

20 The term "halogen" refers to chlorine, fluorine, bromine, and iodine.

The wedge or hash is only one representation of a stereochemical descriptor. All stereoisomers, including enantiomers and diastereomers, are included within Formulas 1-8 and are provided by this invention. When specific isomers are drawn, they are the preferred isomers.

25 In some situations, compounds may exist as tautomers. All tautomers are included within Formulas 1-8 and are provided by this invention.

When compounds are administered, some metabolism may occur. All metabolites are included within Formulas 1-8 and are provided by this invention.

When a bond to a substituent is shown to cross the bond connecting
 30 2 atoms in a ring, then such substituent may be bonded to any atom in the ring, provided the atom will accept the substituent without violating its valency. When there appears to be several atoms of the substituent that may bond to the ring atom, then it is the first atom of the listed substituent that is attached to the ring.

-46-

When a bond is represented by a line such as “---,” this is meant to represent that the bond may be absent or present provided that the resultant compound is stable and of satisfactory valency.

5 Compounds of the present invention are capable of forming acid addition salts (see for example, Berge S.M., et al., “Pharmaceutical Salts,” *Journal of Pharmaceutical Science*, 1977:1-10) with inorganic acids such as, for example, hydrochloric acid, sulfuric acid and the like, as well as salts derived from organic acids such as, for example, aliphatic mono and dicarboxylic acids or aliphatic and aromatic sulphonic acids. The acid addition salts are prepared by contacting the
10 free base form with a sufficient amount of the desired acid to produce the salt. The free base form may be regenerated by contacting the salt form with a base. While the free base more may differ from the salt form in terms of physical properties, such as solubility, the salts are equivalent to their respective free bases for the purposes of the present invention.

15 Certain compounds of the present invention can exist in unsolvated form as well as solvated form including hydrated form. In general, the solvated form including hydrated form is equivalent to unsolvated form and is intended to be encompassed within the scope of the present invention.

20 “Prodrugs” are intended to include any covalently bonded carrier which releases the active parent drug according to Formulas 1-8 in vivo. Examples of prodrugs include acetates, formates, benzoate derivatives of alcohols and amines present in compounds of Formulas 1-8. They also include derivatives of the amidine or guanine functionality and would include $C(=NR_3)NH_2$ where R_3 is selected from OH, NH_2 , C_{1-4} alkoxy, C_{6-10} aryloxy, C_{1-10} alkoxycarbonyl, C_{6-10} aryloxycarbonyl. Preferred derivatives include examples wherein R_3 is OH,
25 NH_2 , methoxy, and ethoxycarbonyl.

The following table provides a list of abbreviations and definitions thereof used in the present invention.

-47-

Abbreviation	Description
AMC	aminomethylcoumarin
aPTT	activated partial thromboplastin time
BOC	tertiary-butyloxycarbonyl
BOP-reagent	benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate
Bz	benzoate
CDCl ₃	deuteriochloroform
DMF	dimethyl formamide
DMSO	dimethylsulfoxide
¹ H-NMR	proton nuclear magnetic resonance
HCl	hydrogen chloride
HF	hydrogen fluoride
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
MOT	mean occlusion time
MS(APCI)	mass spectrometry (atmospheric pressure CI)
MS(CI)	mass spectrometry (chemical ionization)
MS(ES)	mass spectrometry (electro spray)
NaOH	sodium hydroxide
nBuLi	n-butyl lithium
NH ₄ Cl	ammonium chloride
Pd/C	palladium on carbon
PtO ₂	platinum oxide
r.t. or RT	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TT	thrombin time
VAZO-52	2,2'-Azobis-2-methylvaleronitrile

-48-

Also provided by this invention is a method for preventing and treating acute, subacute, and chronic thrombotic disorder in a mammal comprising administering to such mammal an effective amount of a compound of Formulas 1-8. The compounds are useful as anticoagulants for the treatment and prophylaxis of disorders such as venous and arterial thrombosis, pulmonary embolism, and ischemic events such as myocardial infarction or cerebral infarction. These compounds also have therapeutic utility for the prevention and treatment of complications of indwelling vascular access ports and arteriovenous shunts and coagulopathies associated with cardiopulmonary bypass or other extracorporeal systems. These compounds are useful for preventing or treating unstable angina, refractory angina, intermittent claudication, disseminated intravascular coagulation, and ocular buildup of fibrin. Since thrombin and serine proteases have also been demonstrated to activate a number of different cell types, these compounds are useful for the treatment or prophylaxis of septic shock and other inflammatory responses such as acute or chronic atherosclerosis. The compounds also have utility in treating neoplasia/metastasis and neurodegenerative diseases such as Alzheimer's and Parkinson's disease. In a preferred method, the thrombotic disorder is selected from venous thrombosis, arterial thrombosis, pulmonary embolism, myocardial infarction, cerebral infarction, angina, cancer, diabetes. A further embodiment of this invention is a pharmaceutical formulation comprising a compound of Formulas 1-8 administered with a diluent, excipient, or carrier thereof.

PREPARATION OF COMPOUNDS OF THE INVENTION

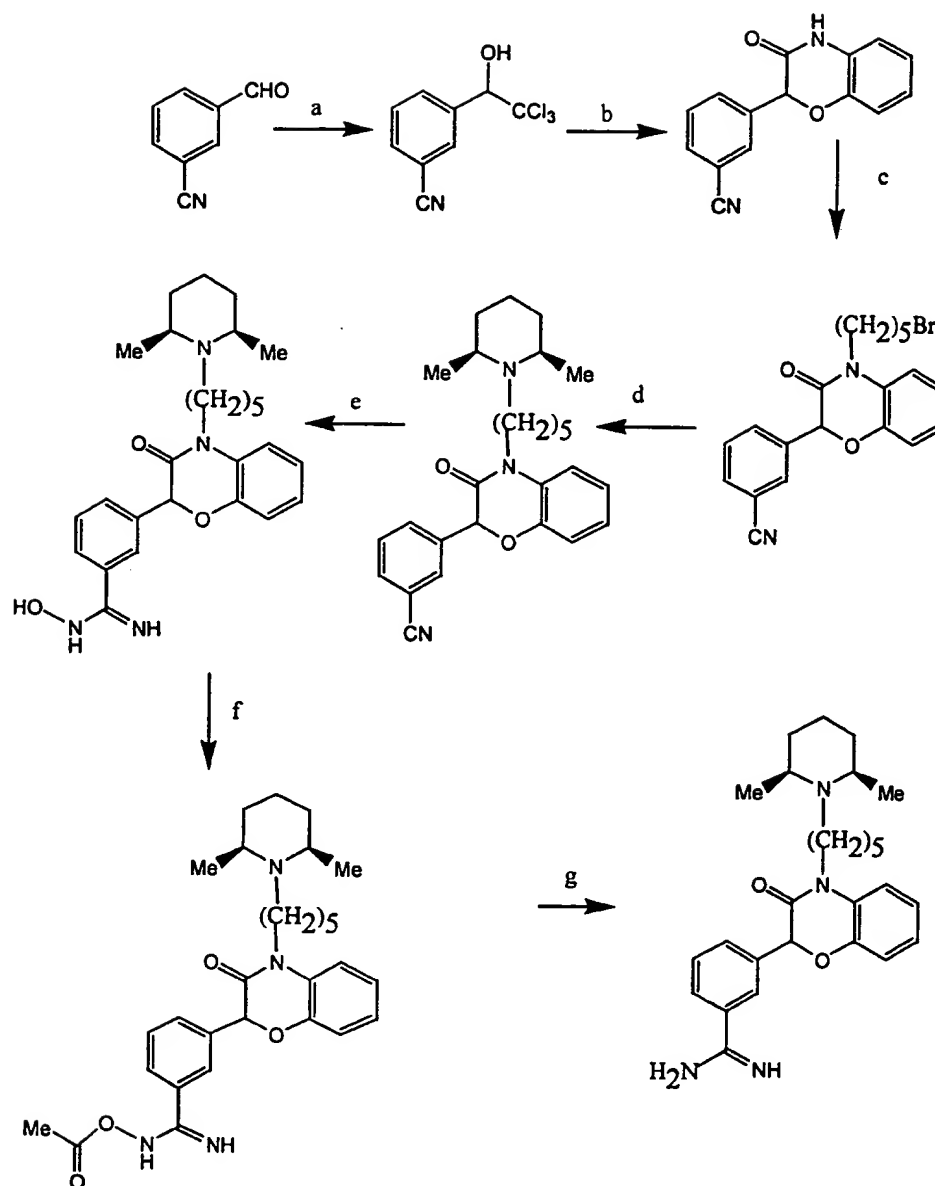
The compounds of Formulas 1-8 can be prepared by any of various methods known to those skilled in the art of organic chemistry. The following general schemes represent preferred routes to provide the compounds of this disclosure. The reactions are typically performed in solvents appropriate to the reagents and substrates employed. It is understood that functionality present in the molecule must be compatible with the reagents and reaction conditions proposed. Not all compounds of Formulas 1-8 falling into a given class may be compatible

-49-

with some of the reaction conditions described. Such restrictions are readily apparent to those skilled in the art of organic synthesis, and alternative methods must then be used.

-50-

Scheme 1



Step a:

5 The aldehyde is converted to the trichloromethyl carbinol by treatment with carbon tetrachloride and aluminum/lead bromide DMF at room temperature according to the procedure of Tanaka J., *Org. Chem.*, 1989:444. Alternative procedures include the addition of trimethylsilyl trichloromethane and tetrabutylammonium fluoride or more typically chloroform and potassium hydroxide as exemplified by Galun, *Org. Synth. Coll.*, 1973;V:130. It should also

-51-

be noted that trimethylsilyl trichloroacetate in the presence of potassium fluoride is an effective process for the preparation of trichlormethylcarbinols as exemplified by Weissman, *Org. Proced. Int.*, 1995;27(5):590-592.

Step b:

5 Addition of o-aminophenol and base affords the benzoxazinone in a manner similar to the procedure of Gukasyan et al., *Arm. Khim. Zh.*, 1988;41(9):572-575. This typically involves treatment of the trichloromethyl carbinol with a suitably substituted ortho-amino phenol in a solvent such as DMF or DMSO in the presence of potassium hydroxide or sodium hydride at room
10 temperature to 100°C. It is apparent that by employing chiral trichloromethyl carbinol, the resulting benzoxazinone will be obtained in chiral form.

Step c:

 Alkylation is typically achieved by treatment with an appropriate electrophile and by the addition of a base in a dipolar aprotic solvent. Typical
15 conditions include, for example, use of a bis-electrophilic substrate such as 1,5-dibromopentane in a dipolar aprotic solvent such as DMF or DMSO and addition of a base, such as sodium hydride. Alternatively, alkylation can be achieved by the addition of a phase transfer reagent such as an alkylammonium salt, such as benzyltriethylammonium chloride, and employing a base such as
20 sodium ethoxide. Reaction rates are typically improved by the application of heat, and hence, reactions are run at from 0°C to 70°C.

Step d:

 Treatment with an amine, such as *cis*-2,6-dimethylpiperidine at an elevated temperature such as 50°C affords the expected N-alkylated piperidine. The amine
25 may be used as solvent, or alternatively, the amine may be added in stoichiometric proportions and the reaction mixture refluxed in a solvent such as ethanol, acetonitrile, or toluene. The product, as the appropriate acid addition salt, is then neutralized by the addition of base such as aqueous potassium hydroxide. In situations where the amine is volatile, then the reaction mixture is heated,
30 typically from 50°C to 150°C, in a sealed tube.

-52-

Step e:

Conversion of the nitrile to the hydroxyamidine is achieved by allowing the nitrile to react with hydroxylamine in methanol at room temperature.

Typically, hydroxylamine hydrochloride is added to the nitrile containing
5 substrate at room temperature, and the reaction is initiated by the addition of base such as potassium carbonate or diisopropylethylamine. The reaction is usually monitored by HPLC to determine the absence of starting material, the nitrile, and are typically complete within a 24-hour period.

Step f:

10 The amidoxime is activated by the addition of acetic anhydride or trifluoroacetic anhydride intermediate in a solvent such as acetic acid or trifluoroacetic acid to afford the O-acylated intermediate, which may be isolated or alternatively used directly in the subsequent reduction step. This step and the subsequent reduction may be combined, i.e., the reduction with Pd/C is performed
15 in acetic anhydride/acetic acid, or trifluoroacetic anhydride/trifluoroacetic acid.

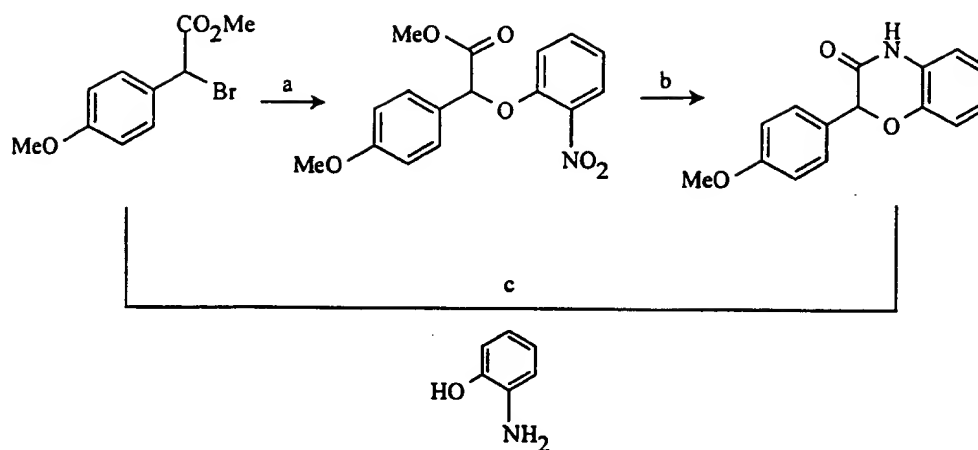
Step g:

The substrate is dissolved in methanol, or acetic acid, or trifluoroacetic acid, and treated with a transition metal catalyst such as Palladium dispersed on carbon and is then hydrogenated briefly, typically for 1 to 12 hours. The product is
20 then isolated, typically by crystallization or via chromatography such as reverse phase HPLC.

Alternative procedures for the synthesis of the parent benzoxazinone include, for example in scheme 2:

-53-

Scheme 2



Step a:

Treatment of the methyl alpha-bromo phenylacetate with ortho-nitrophenol and base readily affords the phenolic ether. Of course, it is realized that activation of the benzylic carbon as a chloride or mesylate would also suffice to allow the initial etherification to proceed. Typically, the potassium or sodium salt of ortho-nitrophenol is added to the electrophile in a solvent, such as DMF, and the mixture warmed, typically to 50°C, until the reaction is judged complete by TLC. Use of a chiral alpha-functionalized aryl acetate would afford the chiral adduct.

Step b:

Reduction of the nitro group to the corresponding aniline is readily achieved with a transition metal such as palladium on carbon or Raney nickel and hydrogen or alternatively by treatment with tin in aqueous hydrochloric acid. These anilines readily cyclize to the corresponding benzoxazinone during the reduction or upon warming in a solvent such as methanol.

Step c:

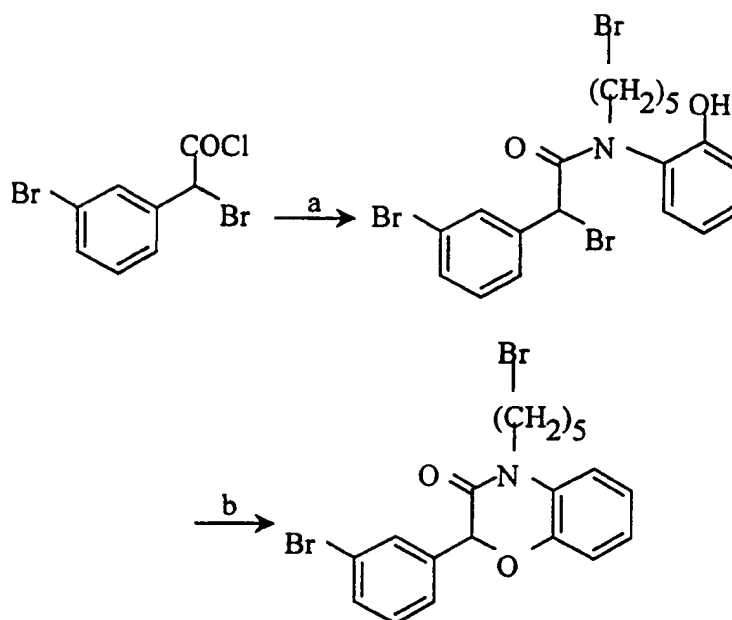
Alternatively upon addition of ortho-aminophenol according to the procedure of *Bull. Soc. Chim. Belg.*, 1987:473-480, the benzoxazine-2-one is isolated directly.

-54-

A further alternative procedure for the preparation of the requisite benzoxazinones requires the treatment of the substituted amino phenol with the acid chloride as shown in Scheme 3 in a manner similar to that described by Krapcho, Tawada et al., *Chem. Pharm. Bull.*, 1990:1238-1245.

-55-

Scheme 3

**Step a:**

5 The ortho amino phenol is treated with the acid chloride in a solvent such as dichloromethane in the presence of a base such as diisopropylethylamine to afford the N-acylated product.

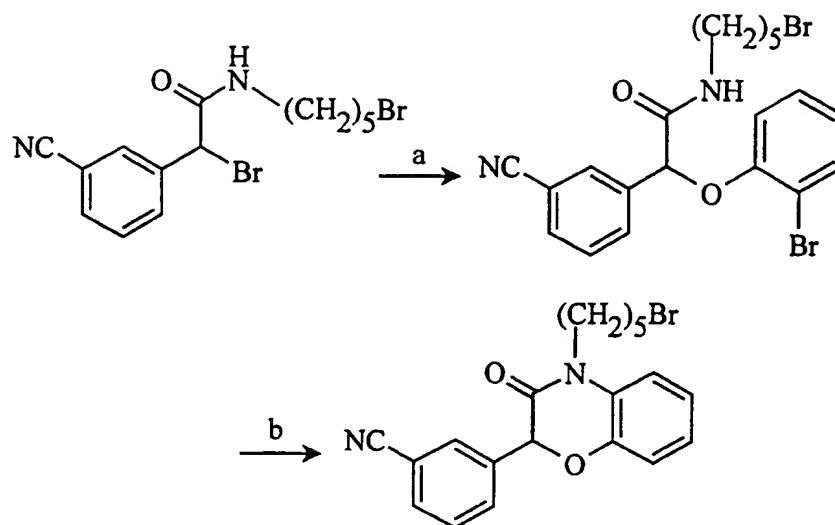
Step b:

10 Treatment with a base such as potassium carbonate in a solvent such as DMF then affords the parent benzoxazinone via an intramolecular nucleophilic addition of the phenoxide to the secondary bromide.

15 A further alternative procedure is outlined in Scheme 4 which is initiated by etherification of an ortho-halo phenol with an alpha-bromo phenylacetamide. Subsequent intramolecular nucleophilic substitution then affords the N-alkylated benzoxazinone (Coutts and Southcott J., *Chem. Soc., Perkin Trans. 1*, 1990:767-771).

-56-

Scheme 4

**Step a:**

5 The sodium salt of the phenol is treated with the electrophile in a solvent such as methylene chloride or dioxane, and then the reaction mixture is warmed to 100°C for 4 hours.

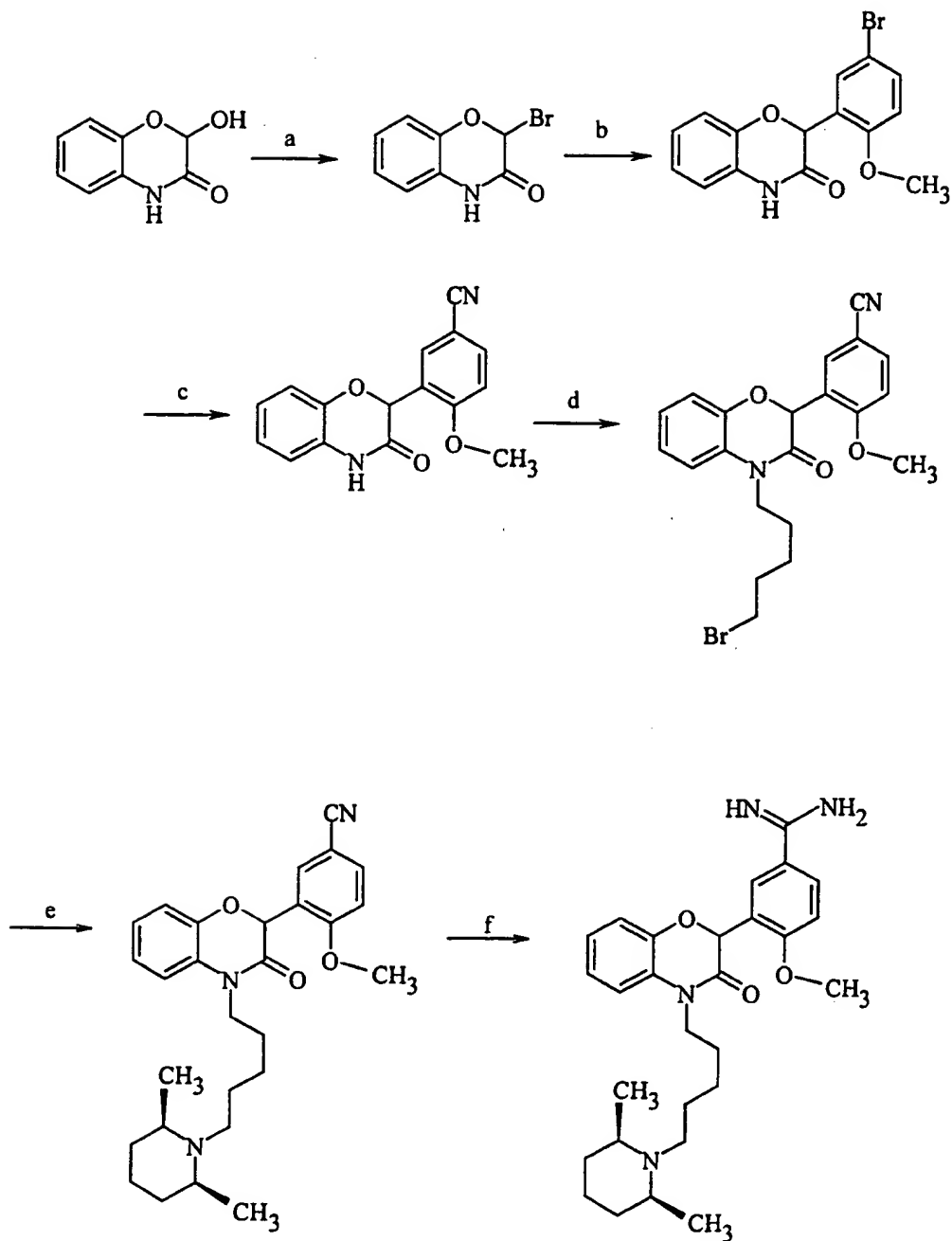
Step b:

Addition of sodium hydride in a solvent such as DMPU and warming to 100°C affords the required benzoxazinone.

10 Scheme 5 demonstrates another alternative procedure that may be employed.

-57-

Scheme 5



Step a:

2-Hydroxy-2H-1,4-benzoxazin-3(4H)-one is prepared by the procedures of
 Sahu A., *Indian Journal of Chemistry*, 1990;603-605, or Matlin SA, *JCS Perkin*

-58-

Trans I, 1979;2481-2487 and is then treated with HBr in acetic acid/acetic anhydride to afford 2-bromo-2*H*-1,4-benzoxazin-3(4*H*)-one at room temperature for 24 to 48 hours, according to the procedure of Tietze LF, *Synthesis*, 1991;1118-1120. The product precipitates from the reaction mixture and due to its hydrolytic
5 instability is used directly in the subsequent reaction step. Alternatively the acetate may be prepared by treating the alcohol with acetic anhydride in the presence of pyridine and catalytic DMAP. Addition of HBr in acetic acid to this acetate again affords the corresponding bromide.

Step b:

10 Addition of a phenol or phenolic ether, such as 4-bromo anisole and a Lewis acid, such as tin (IV) chloride or aluminum (III) chloride, affords after refluxing for several hours the corresponding 2-aryl substituted benzoxazinone.

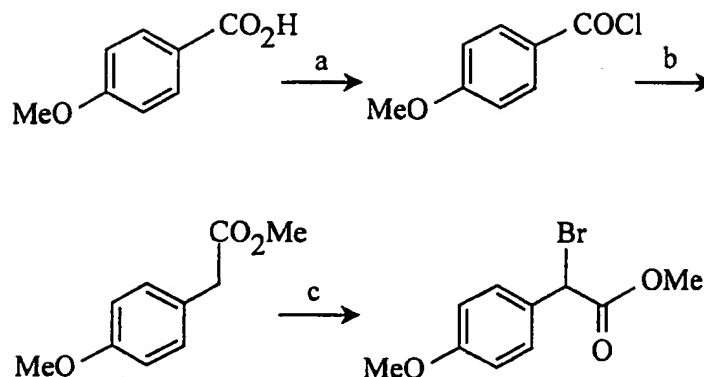
Steps c-f:

 Performed in a manner similar to the previous schemes

15 The substituted alpha-bromo phenylacetates used in these reactions are prepared by a number of standard procedures such as those shown in Scheme 6.

-59-

Scheme 6

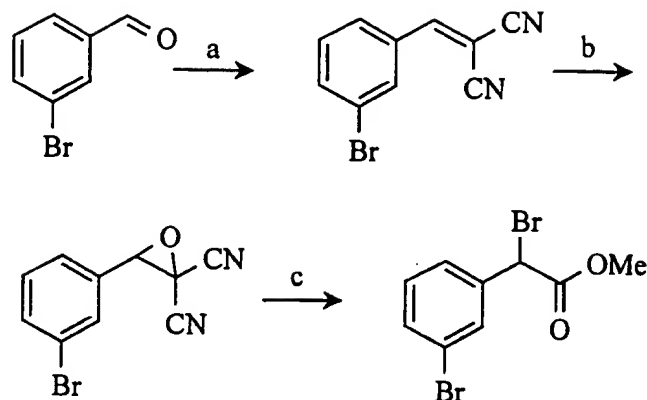


Acetic acid derivatives are prepared by conversion of the substituted
5 benzoic acid to the corresponding acid chloride with, for example, oxalyl chloride
and catalytic DMF and is then treated with ethereal diazomethane. Rearrangement
with silver oxide in an alcoholic solvent, such as methanol, affords the
homologated acetic acid methyl ester. Functionalisation of the alpha position is
10 then achieved by refluxing a solution of the ester in carbon tetrachloride with
N-bromosuccinimide in the presence of a radical initiator such as AIBN. It is also
readily apparent that treatment of acetic acid derivatives with bromine in the
presence of phosphorus tribromide will afford the alpha-bromo phenyl acetate in a
manner similar to the named reaction Hell-Volhard-Zelinskii.

Alternatively, the intermediate alpha bromo ester may be prepared by the
15 procedure shown in Scheme 7 according to the procedure of Robert A.,
Jaguelin S., Guinamant J.L. "Synthesis of esters of α -halo acids from gem
dicyano epoxides. *Tetrahedron*, 1986;42(8):2275-2281.

-60-

Scheme 7

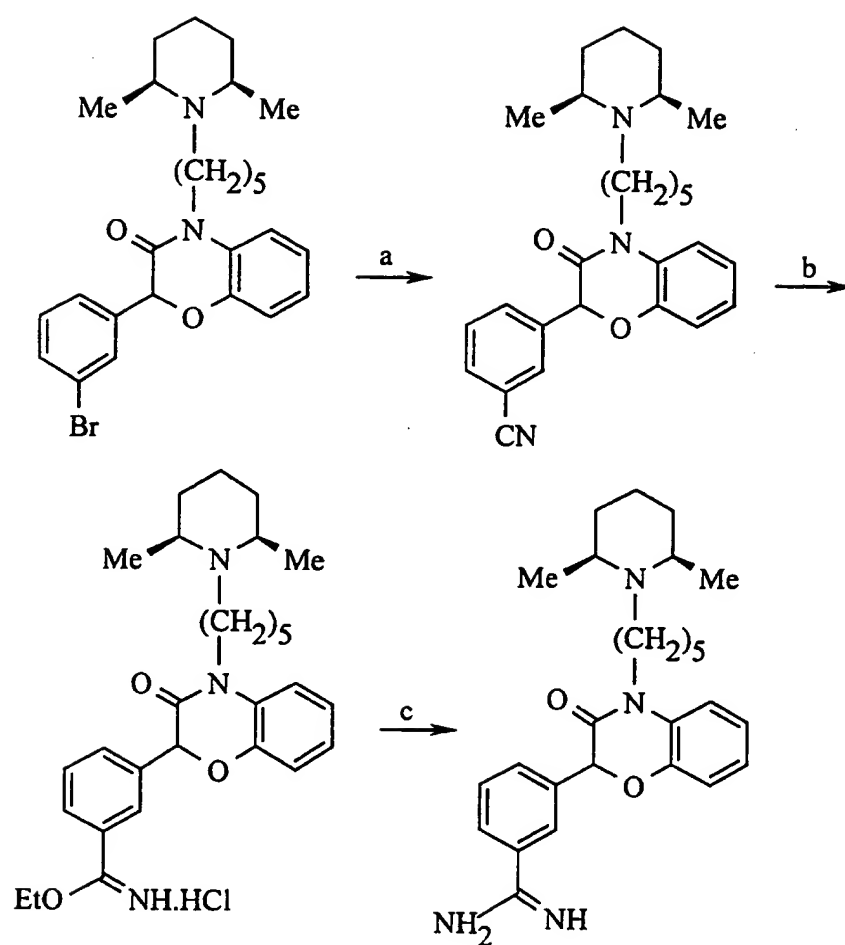


5 In this situation the aldehyde, such as 3-bromobenzaldehyde as a representative example, is reacted with malononitrile in the presence of catalytic piperidine in a solvent such as dioxane to afford the 2-[(3-bromophenyl)-methylene]malononitrile. Epoxide formation proceeds readily with commercial bleach at a pH of 5 to 6. Treatment with hydrobromic acid in methanol then affords the required methyl 2-bromo-2-(3-bromophenyl)acetate. Similarly
10 prepared was methyl 2-bromo-2-(3-cyanophenyl)acetate

Alternative procedures for the conversion of nitriles to amidines are also available as shown in Scheme 8. The nitrile in turn are available by, for example, a palladium catalyzed cross-coupling reaction with $\text{Zn}(\text{CN})_2$ or via treatment of the aryl bromide at elevated temperatures with copper (I) cyanide. Treatment of
15 the nitrile with hydrogen chloride in an alcoholic solvent affords the corresponding iminoether hydrochloride. These intermediates are then treated with source of ammonia, for example ammonia in methanol, or ammonium chloride, or ammonium acetate, and the mixture is stirred, and warmed if necessary, to afford the amidine.

-61-

Scheme 8



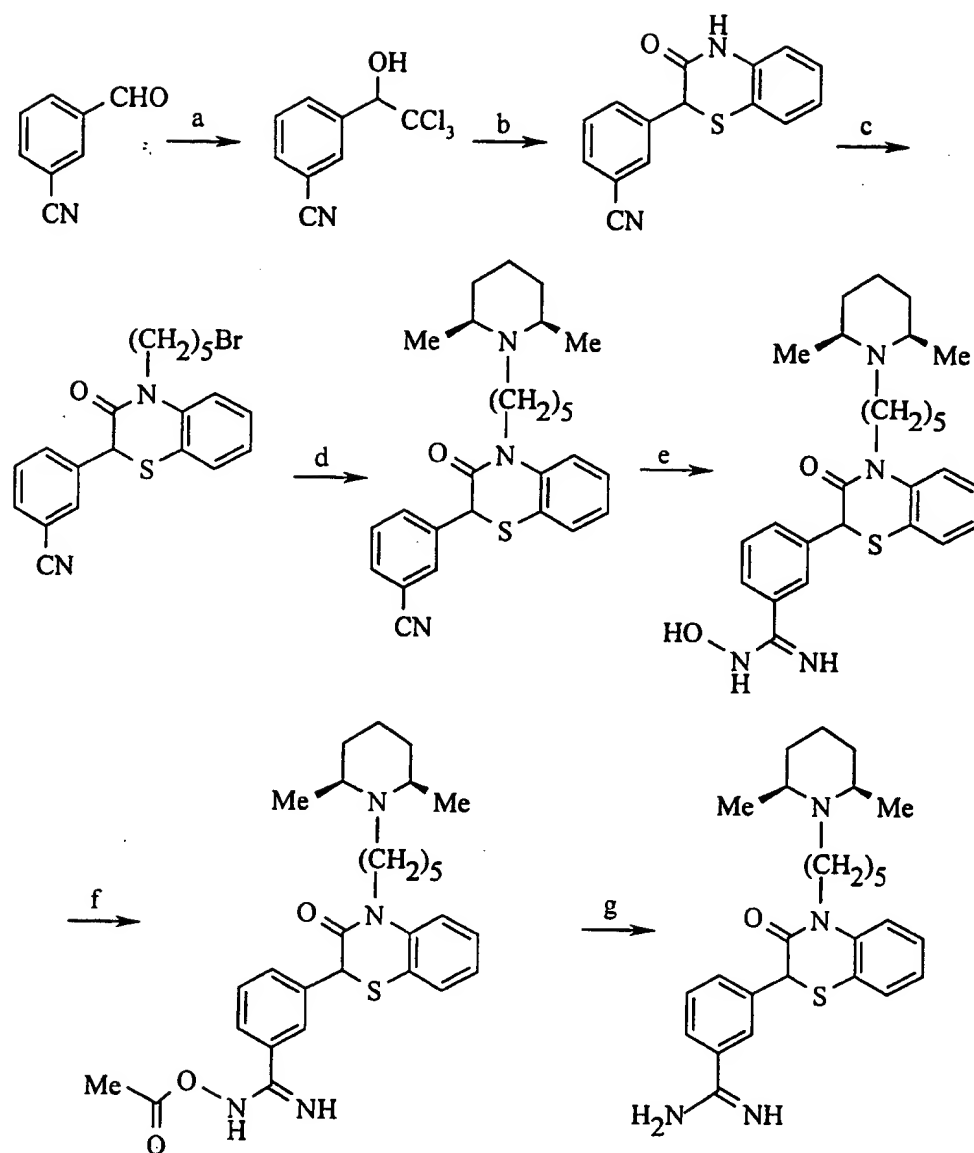
The benzothiazinone of Formula 1 may also be prepared according to

5

Scheme 9.

-62-

Scheme 9



The reaction sequence is similar to that described in Scheme 1 except that 2-aminophenyl thiol replaces 2-aminophenol in the initial reaction sequence.

5

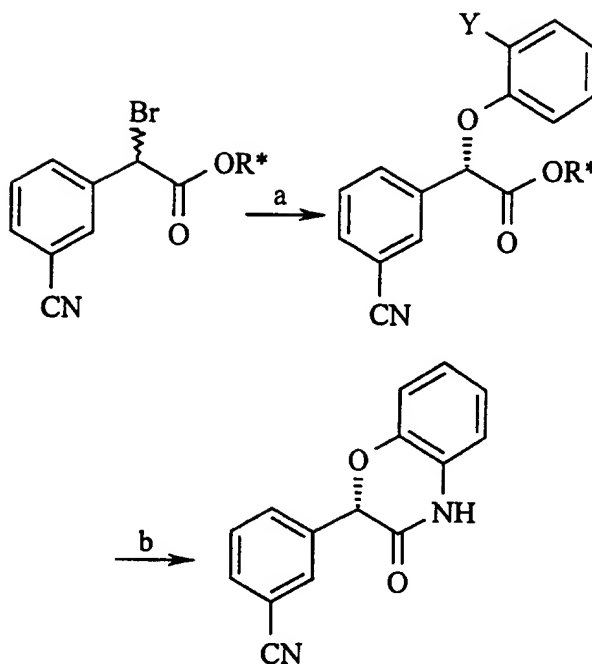
Since some of the compounds of Formula 1 exist as a mixture of enantiomers, it is often desirable to prepare the optically pure material. In these

-63-

situations, the addition salts with chiral acids are prepared and the mixture separated by crystallization. The parent compounds may then be liberated by treatment with base, such as potassium hydroxide. Enantiomers may also be separated by chiral HPLC. Suitable columns for separating enantiomers of intermediates such as 3-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarbonitrile include beta-cyclodextrin (keystone chiral β -PM) employing 50% water and acetonitrile mixtures. Alternatively, an asymmetric synthesis may be employed for the synthesis of a specific enantiomer. In particular, a suitably substituted phenoxide (for benzoxazinones) or thiophenoxide (for benzothiazinones) may be added to a pentolactone derivative, as described by Koh, *J. Org. Chem.*, 1994;59:4683-4686 and outlined in Scheme 10.

-64-

Scheme 10

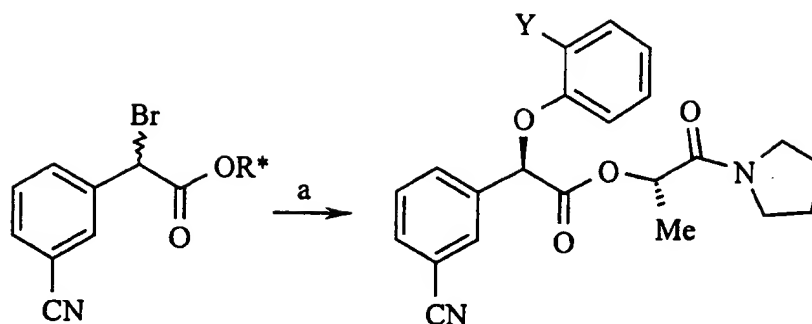


Use of (R) pantolactone esters affords the (S) diastereomer. In this scheme, Y is a substituent that may be elaborated to afford an aniline which undergoes intramolecular cyclization to afford the required chiral benzoxazinone. Examples of such substituents would include a nitro functionality or N-acetyl group.

A further alternative procedure for the generation of chiral benzoxazinone intermediates is available by application of lactamide derived esters of racemic alpha-halo carboxylic acids (Devine, *Tetrahedron Letts.*, 1996:2683-2686) as outlined in Scheme 11.

-65-

Scheme 11



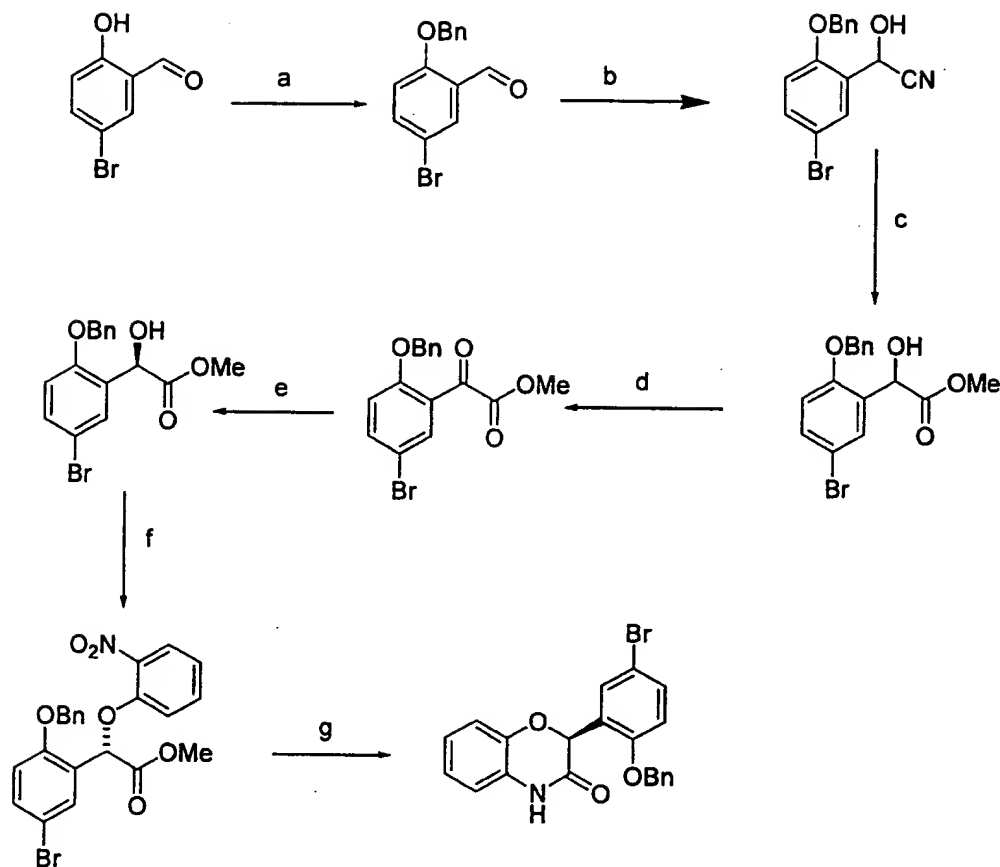
The diastereoselectivity of this reaction is good, and the products are of the (R) stereochemistry providing a complementary approach to that of Scheme 10.

5 It should be noted that chiral alpha-trichloromethyl carbinols afford optically active alpha-aryloxy acids upon treatment with phenoxide providing yet another alternative method to preparing chiral benzoxazinones or benzothiazinones (Corey, *Tetrahedron Lett.*, 1992:3431).

10 Another procedure for preparing chiral benzoxazinones is outlined in Scheme 12

-66-

Scheme 12



Step a:

5 The aldehyde is protected via the formation of a suitable protecting group, which in the above scenario is a benzylether, with for example potassium carbonate or sodium hydroxide and benzyl bromide in a solvent such as DMF or ethanol.

Step b:

10 Addition of cyanide to the aldehyde readily forms the intermediate cyano hydrin in a solvent such as methanol. It is envisioned that this process may also be performed in an asymmetric manner by use of any one of the following general procedures Danda, H et al., *Chem Lett* 1991, 731. Poly(quinidine-co-acrylonitrile) Effenberg, F et al., *Tetrahedron Lett* 1990, 31 (9), 1249. (Oxynitrilase) Mori, A. et al., *Chem Lett* 1989 (12), 2119. Cyclo-(Leu-His) or Tanaka, K. et al., *J*
 15 *Org Chem* 1990, 55, 181. cyclo((S)-Phe-(S)-His)

-67-

Minamikawa, H. et al., *Bull Chem Soc Jpn* 1988, 61 (12), 4379. 1,1,4,4-Tetraphenylbutanetetraol-(2R,3R)-O,O-phenylethylidene Ti(i-PrO)₂Cl₂
Harrington, K. J et al., *Aust J Chem* 1986, 39, 1135. 1) beta-Cyclodextrin

5 Steps c:

Conversion of the cyano functional group to a methyl ester is readily achieved by treatment of the nitrile with HCl gas in an alcoholic solvent such as methanol. Addition of water then readily converts the intermediate imino ether to the ester.

10 Step d:

Oxidation of the alcohol to the keto-ester is readily achieved with an oxidising agent such as oxalyl chloride and dimethylsulfoxide or by heating with manganese dioxide in a solvent such as toluene or methylene chloride.

Step e:

15 Chiral reduction of the keto-ester is best achieved with a reducing agent like R-alpine borane. This reduction is typically slow and takes several days to complete.

Step f:

20 A Mitsunobo coupling reaction is then performed on this chiral alcohol employing nitro phenol (or possibly amino phenol), diisopropylazodicarboxylate (or other alkylazodicarboxylate) and triphenylphosphine in a solvent such as ethylacetate at a low temperature such as - 40 °C.

Step g:

25 Reduction of the nitro group is best achieved with neutral Raney Nickel and a hydrogen atmosphere in a solvent such as methanol. It is important that the solution does not become basic since a reduction in enantiomeric excess may be observed.

-68-

Compounds of the present invention are further characterized by their ability to inhibit the catalytic activity of factor Xa, which is demonstrated in the assay as follows. Compounds of the present invention may be prepared for assay by dissolving them in buffer to give solutions ranging in concentrations from 1 to 100 μ M. In an assay to determine the inhibitory dissociation constant, K_i , for a given compound, a chromogenic or fluorogenic substrate of factor Xa would be added to a solution containing a test compound and factor Xa; the resulting catalytic activity of the enzyme is spectrophotometrically determined. This assay is well-known to those skilled in the art and is commonly used to determine antithrombotic activity.

The compounds of the present invention may be used as anti-coagulants *in vitro* or *ex vivo* as in the case of contact activation with foreign thrombogenic surfaces such as is found in tubing used in extracorporeal shunts. The compounds of the invention may also be used to coat the surface of such thrombogenic conduits. To this end, the compounds of the invention can be prepared as lyophilized powders, redissolved in isotonic saline or similar diluent, and added in an amount sufficient to maintain blood in an anticoagulated state.

The therapeutic agents of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers. The proportion of each carrier is determined by the solubility and chemical nature of the compound, the route of administration, and standard pharmaceutical practice. For example, the compounds may be injected parenterally; this being intramuscularly, intravenously, or subcutaneously. For parenteral administration, the compound may be used in the form of sterile solutions containing other solutes, for example, sufficient saline or glucose to make the solution isotonic. The compounds may be administered orally in the form of tablets, capsules, or granules containing suitable excipients such as starch, lactose, white sugar and the like. The compounds may also be administered sublingually in the form of troches or lozenges in which each active ingredient is mixed with sugar or corn syrups, flavoring agents, and dyes, and then dehydrated sufficiently to make the mixture suitable for pressing into solid form. The compounds may be administered orally in the form of solutions

-69-

which may contain coloring and/or flavoring agents. Typical formulations will contain from about 5% to 95% by weight of an invention compound.

5 The amount of invention compound to be utilized to prevent and treat thrombotic disorders is that amount which is effective to prevent or treat the condition without causing unacceptable side effects. Such effective amounts will be from about 0.01 mg/Kg to about 500 mg/Kg, preferably from about 1 mg/Kg to about 100 mg/Kg. Physicians will determine the precise dosage of the present therapeutic agents which will be most suitable. Dosages may vary with the mode of administration and the particular compound chosen. In addition, the dosage
10 may vary with the particular patient under treatment.

When the composition is administered orally, a larger quantity of the active agent will typically be required to produce the same effect as caused with a smaller quantity given parenterally.

To further assist in understanding the present invention, the following non-limiting examples of such factor Xa inhibitory compounds are provided. The
15 following examples, of course, should not be construed as specifically limiting the present invention, variations presently known or later developed, which would be within the purview of one skilled in the art and considered to fall within the scope of the present invention as described herein. The preferred compounds as of the present invention are synthesized using conventional preparative steps and
20 recovery methods known to those skilled in the art of organic and bio-organic synthesis, while providing a new and unique combination for the overall synthesis of each compound. Preferred synthetic routes for intermediates involved in the synthesis as well as the resulting anti-thrombotic compounds of the present
25 invention follow.

EXAMPLES

In general, evaporation of reaction mixtures were carried out by rotary evaporation in vacuo at room temperature 18°C to 25°C or at elevated
temperatures up to 50°C. Chromatography, preferably by medium pressure liquid
30 chromatography, were generally performed on Merck Kieselgel. Reverse phase

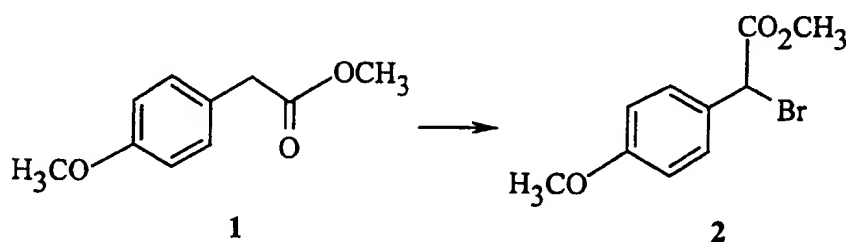
-70-

purification via high pressure liquid chromatography (HPLC), for particular polar compounds, was performed on C-18 reverse phase silica gel employing a gradient elution of water and acetonitrile containing 0.1% trifluoroacetic acid. The final products displayed nuclear magnetic resonance (NMR) spectra and mass spectra consistent with their assigned structure. Intermediates were not typically fully characterized and their purity was routinely assessed by HPLC or thin layer chromatography.

EXAMPLE 1

4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one

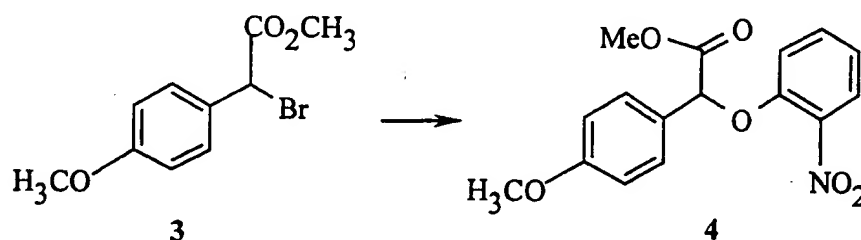
Step (a): Preparation of Methyl 2-bromo-2-(4-methoxyphenyl)acetate



To methyl 4-methoxyphenylacetate (1) (5.0 g, 27.7 mmol) in carbon tetrachloride was added N-bromosuccinimide (5.92 g, 33.3 mmol) and VAZO52 (152 mg, 0.612 mmol). The reaction mixture was stirred and heated at reflux for 3 hours. ¹H NMR indicated complete bromination of the starting material. The mixture was cooled in an ice-bath. The precipitate was filtered and washed with carbon tetrachloride. The filtrate was evaporated in vacuo to give (2) as a brown oil in quantitative yield, and sufficiently pure for subsequent reactions.

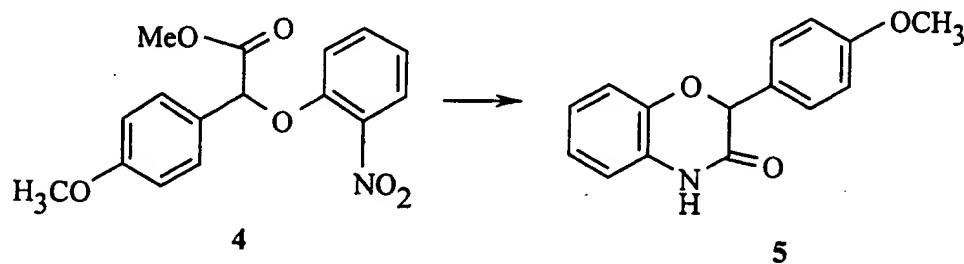
¹H NMR (CDCl₃, 400 MHz): δ 7.44 (2H, d, J=6.84 Hz), 6.84 (2H, d, J=6.71 Hz), 5.31 (1H, s), 3.77 (3H, s), 3.75 (3H, s).

-71-

Step (b): Preparation of Methyl 2-(4-methoxyphenyl)-2-(2-nitrophenoxy)acetate

To (3) (7.18 g, 27.7 mmol) in DMSO (20 mL) was added o-nitrophenol sodium salt (7.32 g, 45.5 mmol). The reaction mixture was stirred at 70°C for 24 hours. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were washed with brine (200 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified on a silica gel column eluted with 20% ethyl acetate in hexane. The product (4) was isolated 2.90 g (33%) as an orange oily solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.88 (1H, m), 7.54-7.44 (3H, m), 6.92-7.11 (4H, m), 5.70 (1H, s), 3.82 (3H, s), 3.72 (3H, s).

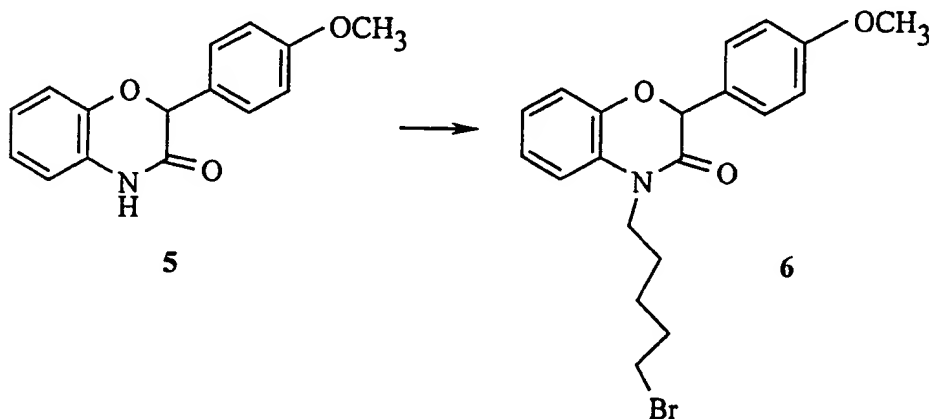
Step (c): Preparation of 2-(4-Methoxyphenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one

The phenolic ether (4) (2.88 g, 9.08 mmol) was hydrogenated over Raney nickel (1 g) in THF (50 mL) and methanol (50 mL) for 23 hours at room temperature. The mixture was filtered and the filter pad washed with methanol and THF. The combined filtrate and washings were evaporated in vacuo to give the benzoxazinone (5) as an orange solid in quantitative yield.

-72-

^1H NMR (CDCl_3 , 300 MHz): δ 7.78 (1H, bs), 7.35 (2H, d, $J=8.79$ Hz), 7.00-6.76 (6H, m), 5.63 (1H, s), 3.77 (3H, s).

Step (d): Preparation of 4-(5-Bromopentyl)-2-(4-methoxyphenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one



5

To the benzoxazinone (5) (2.42 g, 9.48 mmol) in DMF (9 mL) was added sodium hydride (0.433 g, 10.82 mmol), and the solution was stirred at 70°C for 15 minutes until bubbling stopped. To this solution was added 1,5-dibromopentane (8.66 g, 37.7 mmol), and the solution was stirred at 70°C for additional 5 hours. The solution was cooled, diluted with water, and extracted with ethyl acetate (5×200 mL). The combined organic extracts were washed with brine (2×100 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified on a silica gel column eluted with 20% ethyl acetate in hexane. The product (6) was isolated 1.85 g (48%) as a yellow oil.

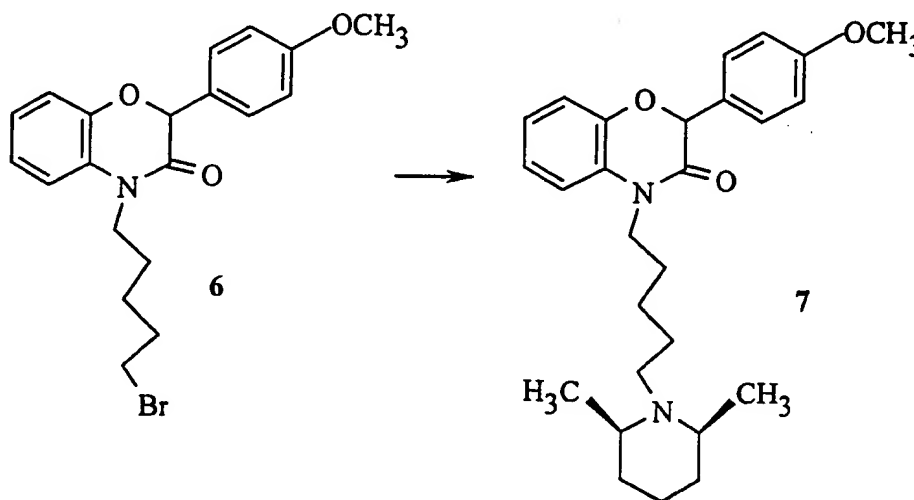
10

^1H NMR (CDCl_3 , 300 MHz): δ 7.26 (2H, d, $J=4.49$ Hz), 7.03-6.96 (4H, m), 6.84 (2H, d, $J=6.68$ Hz), 5.64 (1H, s), 4.12 (2H, m), 3.80 (3H, s), 3.40 (2H, m), 1.96-1.87 (2H, m), 1.75-1.68 (2H, m), 1.61-1.51 (2H, m).

15

-73-

Step (e): Preparation of 4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one



To (6) (0.50 g, 1.23 mmol) was added *cis*-2,6-dimethylpiperidine (2 mL, 14.8 mmol), and the solution was stirred at 50°C for 16 hours. The solution was cooled, diluted with water, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated sodium bicarbonate (2 × 100 mL), washed with brine (2 × 100 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified by preparative HPLC (Vydac 218TP1022 C-18, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 95:5 (i):(ii) to 60:40 (i):(ii) over 90 minutes, flow rate 20 mL/minute, λ = 214 nm) and was lyophilized to give 27 mg (12%) of product (7) as a fluffy white solid.

¹H NMR (CDCl₃, 400 MHz): δ 7.27 (2H, m), 7.03-6.95 (4H, m), 6.84 (2H, m), 5.63 (1H, s), 4.03 (2H, m), 3.77 (3H, s), 3.25 (2H, m), 3.00 (2H, s), 2.72 (2H, m), 2.41 (2H, bs), 2.04 (2H, m), 1.88-1.66 (6H, m), 1.48-1.32 (6H, m).
CI MS $M+1$ = 437.

HPLC: RT = 17.28 min. (Beckman 235328 C-18 5 μ m 4.6 mm × 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and

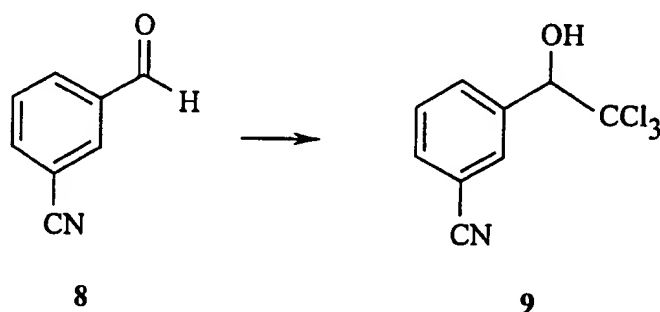
-74-

(ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, $\lambda = 214$ nM).

EXAMPLE 2

5 3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide

Step (a): Preparation of 3-(2,2,2-Trichloro-1-hydroxyethyl)benzonitrile

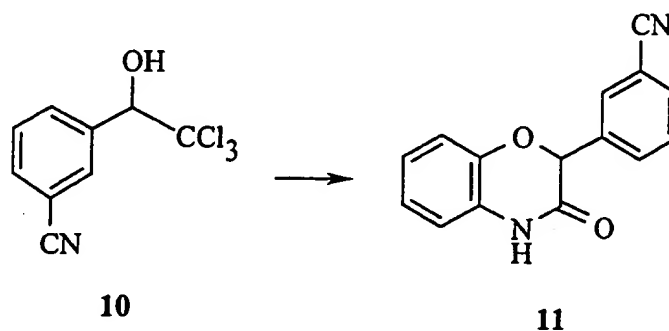


Into a mixture of lead(II) bromide (1.69 g, 4.60 mmol) and finely cut aluminum foil (1.25 g, 45.8 mmol) in DMF (226 mL) was added
 10 3-cyanobenzaldehyde (6.01 g, 45.8 mmol) and carbon tetrachloride (8.84 mL, 91.7 mmol), and the mixture was stirred at ambient temperature 3 hours. The reaction was quenched with aqueous 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic
 15 extracts were washed with brine (200 mL), dried with magnesium sulfate, filtered, evaporated in vacuo, and dried under high vacuum to give the trichloromethyl carbinol (9) as a brown oil in quantitative yield.

¹H NMR (CDCl₃, 300 MHz): δ 7.94 (1H, m), 7.86 (1H, m), 7.66 (1H, m), 7.48 (1H, m), 5.24 (1H, s), 4.98 (1H, bs).

-75-

Step (b): Preparation of 2-(3-Cyanophenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one

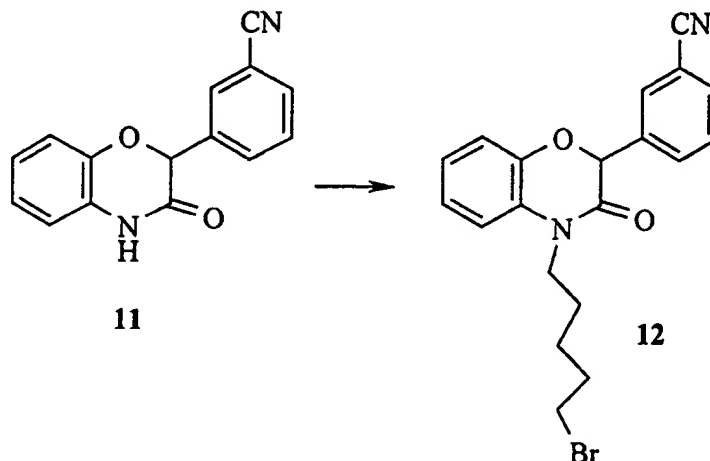


To o-aminophenol hydrochloride (3.29 g, 13.1 mmol) in DMSO (15 mL) was added sodium hydride (2.63 g, 65.8 mmol). After bubbling and evolution of heat ceased, a solution of (**10**) (3.29 g, 13.1 mmol) in DMSO (10 mL) was added dropwise over 15 minutes. After evolution of heat ceased, the mixture was stirred at 70°C for 4 hours. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate (5 × 500 mL). The combined organic extracts were washed with brine (200 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified on a silica gel column eluted with 25% ethyl acetate in dichloromethane. The product (**11**) was isolated 0.55 g (17%) as an orange solid.

¹H NMR (CDCl₃, 300 MHz): δ 8.47 (1H, s), 7.80-7.72 (2H, m), 7.64 (1H, m), 7.49 (1H, m), 7.15-6.97 (3H, m), 6.82 (1H, m), 5.70 (1H, s).

-76-

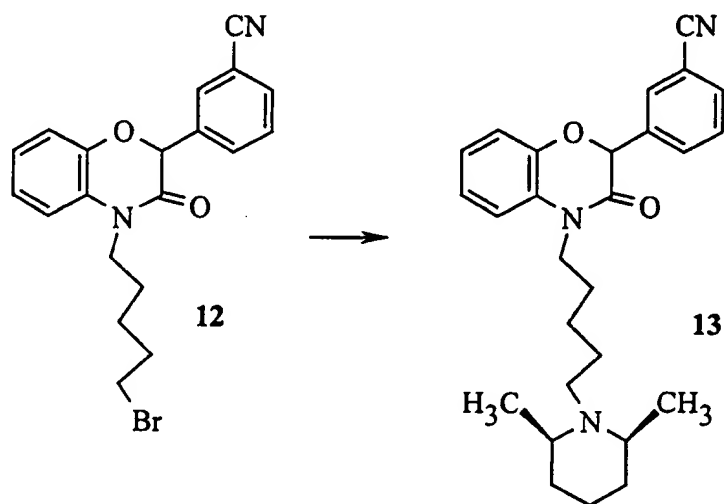
Step (c): Preparation of 4-(5-Bromopentyl)-2-(3-cyanophenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one



To the benzoxazinone (11) (0.72 g, 2.87 mmol) in DMF (5 mL) was
5 added sodium hydride (0.126 g, 3.15 mmol), and the solution was stirred at
70°C for 15 minutes until bubbling stopped. To this solution was added
1,5-dibromopentane (1.57 mL, 11.5 mmol) and the solution was stirred at 70°C
for additional 3 hours. The solution was cooled, diluted with water, and extracted
with ethyl acetate (5 × 200 mL). The combined organic extracts were washed with
10 brine (2 × 100 mL), dried with magnesium sulfate, filtered, and evaporated
in vacuo. The residue was purified on a silica gel column eluted with 20% to 40%
ethyl acetate in hexane. The product (12) was isolated 0.64 (56%) as a yellow oil.
¹H NMR (CDCl₃, 300 MHz): δ 7.71 (2H, m), 7.61 (1H, m), 7.46 (1H, m),
7.12-7.03 (3H, m), 6.97 (1H, m), 5.69 (1H, s), 3.98 (2H, m), 3.41 (2H, m),
15 1.91 (2H, m), 1.71 (2H, m), 1.55 (2H, m).

-77-

Step (d): Preparation of 4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-2-(3-cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one



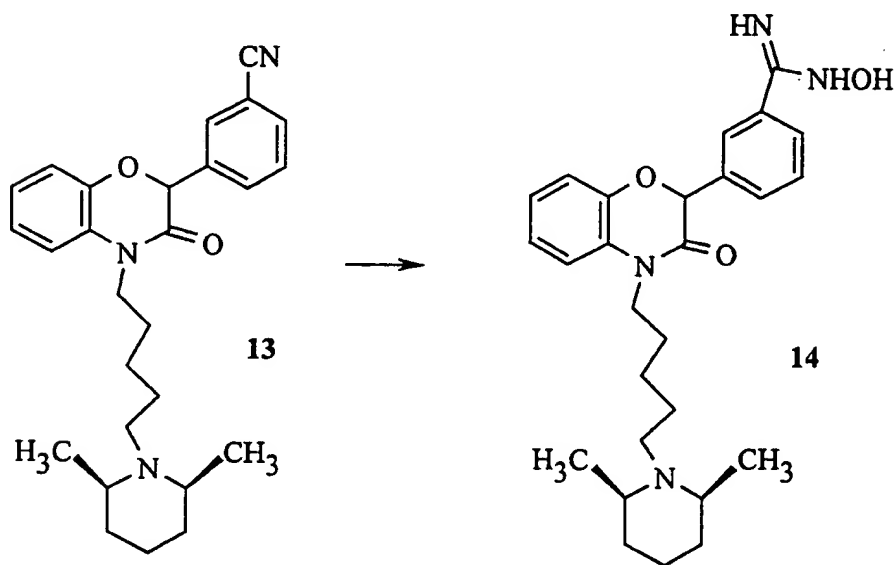
To (12) (1.08 g, 2.70 mmol) was added *cis*-2,6-dimethylpiperidine (8 mL, 60 mmol). The solution was stirred at 70°C for 16 hours. The solution was cooled, diluted with water, and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with saturated sodium bicarbonate (2 × 100 mL), washed with brine (2 × 100 mL), dried with magnesium sulfate, filtered, evaporated in vacuo, coevaporated with toluene, and dried under high vacuum to give 1.09 g (94%) of (13) as a yellow oil.

¹H NMR (CDCl₃, 300 MHz): δ 7.63 (2H, m), 7.54 (1H, m), 7.40 (1H, m), 7.13 (1H, m), 7.03-6.85 (3H, m), 5.63 (1H, s), 3.91 (2H, m), 2.91 (2H, m), 2.70 (2H, m), 2.61-2.06 (4H, m) 1.64-1.18 (8H, bm), 1.06 (6H, m).

HPLC: RT = 13.88 min. (Beckman 235328 C-18 5 μm 4.6 mm × 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

-78-

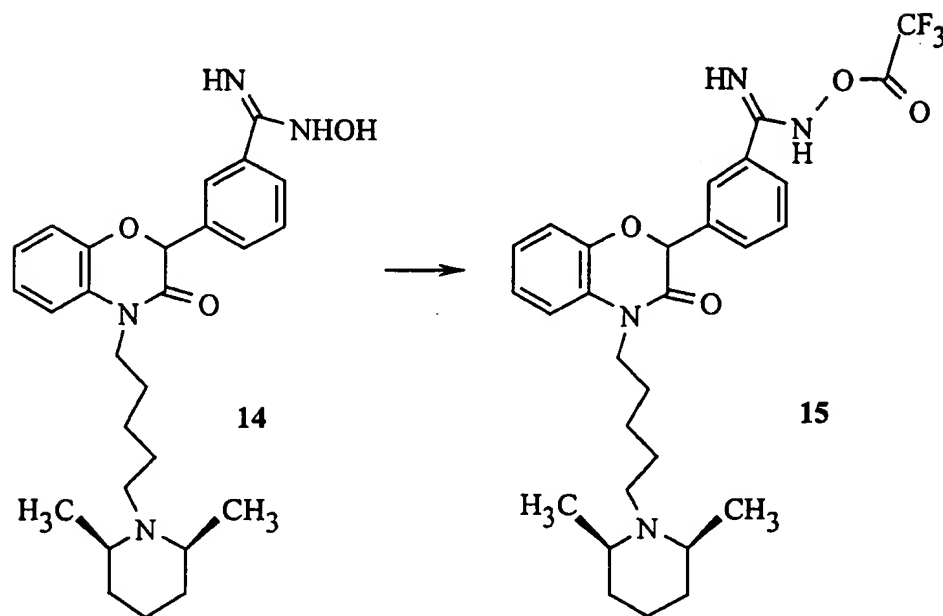
Step (e): Preparation of 3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-*N*-hydroxybenzenecarboximidamide



- 5 To (13) (1.09 g, 2.53 mmol) in methanol (30 mL) were added hydroxylamine hydrochloride (0.438 g, 6.30 mmol) and diisopropylethylamine (0.44 mL, 2.53 mmol). The solution was stirred at room temperature for 16 hours. The solvent was evaporated in vacuo, and the oil was dried under high vacuum to give (14) in quantitative yield.
- 10 HPLC: RT = 8.39 min. (Beckman 235328 C-18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nM).

-79-

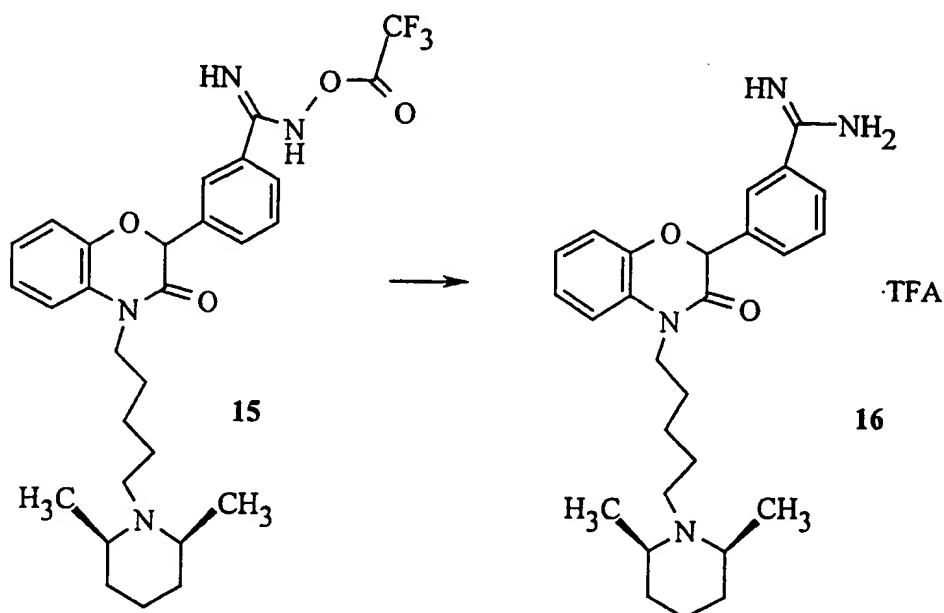
Step (f): Preparation of 3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-*N*-hydroxytrifluoroacetatebenzenecarboximidamide



- 5 To (14) (0.53 g, 1.14 mmol) was added trifluoroacetic anhydride (7 mL), and the solution was stirred at room temperature for 2 hours. The solvent was removed in vacuo to give (15) as a yellow oil in quantitative yield.
- HPLC: RT = 17.44 min. (Beckman 235328 C-18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and
- 10 (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

-80-

Step (g): Preparation of 3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide



- 5 To (15) (0.57 g, 1.13 mmol) in trifluoroacetic acid (16 mL) was added 20% palladium on carbon (0.1 g), and the mixture was hydrogenated at 23°C for 48 hours. The mixture was filtered and the filter pad washed with trifluoroacetic acid. The combined filtrate and washings were evaporated in vacuo, and the residue was purified by preparative HPLC (Vydac 218TP1022 C-18, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and
- 10 (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 95:5 (i):(ii) to 60:40 (i):(ii) over 90 minutes, flow rate 20 mL/minute, $\lambda = 214$ nM) and lyophilized to give 251 mg (50%) of the bis TFA salt of (16). To (16) in acetonitrile (2 mL) and water (2 mL) was added Amberlite® IRA-400(Cl) ion exchange resin (3.36 g).
- 15 The mixture was filtered, and the filtrate was lyophilized to give 155 mg (26%) of the bis hydrochloride salt (16).

^1H NMR (CDCl_3 , 300 MHz): δ 9.44 (1H, s), 9.19 (2H, s), 7.80 (2H, m), 7.64 (2H, m), 7.28 (1H, m), 7.11-7.01 (3H, m), 5.93 (1H, s), 3.97 (2H, m), 3.18 (2H, bs), 3.03 (2H, bs), 1.75-1.36 (12H, bm), 1.23 (6H, m).

-81-

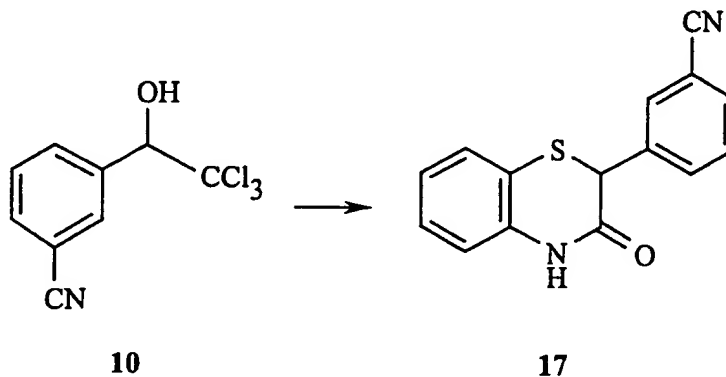
CI MS M+1 = 449.

HPLC: RT = 8.26. (Beckman 235328 C-18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

EXAMPLE 3

3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-benzenecarboximidamide

Step (a): Preparation of 2-(3-Cyanophenyl)-3,4-dihydro-2*H*-1,4-benzothiazin-3-one

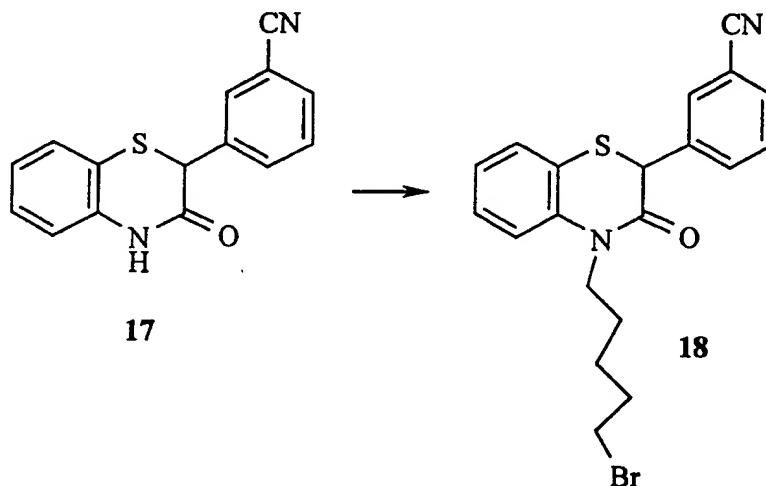


To o-aminothiophenol (2.39 mL, 22.3 mmol) in DMF (60 mL) was added sodium hydride (3.61 g, 90.3 mmol). After bubbling and evolution of heat ceased, a solution of (10) (5.67 g, 22.6 mmol) in DMSO (40 mL) was added dropwise over 15 minutes. After evolution of heat ceased, the mixture was stirred at 50°C for 6 hours and at room temperature for 16 hours. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate (5 \times 500 mL). The combined organic extracts were washed with brine (200 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was absorbed onto silica gel and purified on a silica gel column eluted with 1% to 4% methanol in dichloromethane. The residue was crystallized from ethyl acetate and hexane to give 1.71 g (29%) of product (17) as a tan solid.

-82-

^1H NMR (CDCl_3 , 300 MHz): δ 10.97 (1H, s), 7.75 (1H, m), 7.57 (2H, m), 7.32 (1H, m), 7.20 (1H, m), 7.00 (3H, m), 5.10 (1H, s).

Step (b): Preparation of 4-(5-Bromopentyl)-2-(3-cyanophenyl)-3,4-dihydro-2H-1,4-benzothiazin-3-one



5

To the benzothiazinone (17) (0.75 g, 2.82 mmol) in DMF (5 mL) was added sodium hydride (0.124 g, 3.09 mmol), and the solution was stirred at 70°C for 15 minutes until bubbling stopped. To this solution was added 1,5-dibromopentane (1.54 mL, 11.2 mmol), and the solution was stirred at 70°C for additional 16 hours. The solution was cooled, diluted with water, and extracted with ethyl acetate (3 \times 300 mL). The combined organic extracts were washed with brine (2 \times 100 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified on a silica gel column eluted with 20% to 30% ethyl acetate in hexane. The product (18) was isolated 0.66 (52%) as a yellow oil.

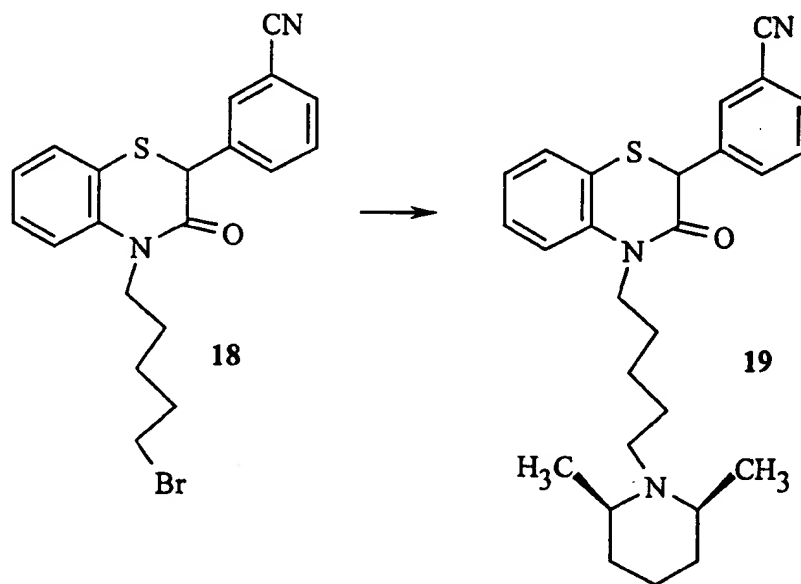
10

^1H NMR (CDCl_3 , 300 MHz): δ 7.57 (3H, m), 7.38 (2H, m), 7.25 (1H, m), 7.11-7.01 (2H, m), 4.64 (1H, s), 4.09 (2H, m), 3.40 (2H, m), 1.91 (2H, m), 1.70 (2H, m), 1.53 (2H, m).

15

-83-

Step (c): Preparation of 4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-2-(3-cyanophenyl)-3,4-dihydro-2*H*-1,4-benzothiazin-3-one



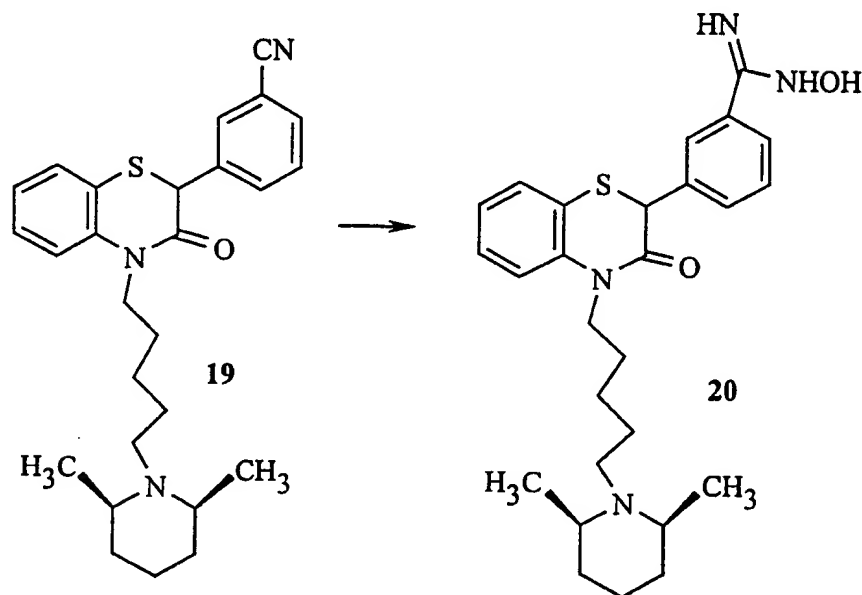
To (18) (0.66 g, 1.59 mmol) was added *cis*-2,6-dimethylpiperidine (6.0 mL, 44 mmol). The solution was stirred at 70°C for 48 hours. The solution was cooled, diluted with water, and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with saturated sodium bicarbonate (2 × 100 mL), washed with brine (2 × 100 mL), dried with magnesium sulfate, filtered, evaporated in vacuo, coevaporated with toluene, and dried under high vacuum to give 0.69 g (97%) of (19) as a yellow oil.

¹H NMR (CDCl₃, 300 MHz): δ 7.55 (3H, m), 7.37 (2H, m), 7.24 (1H, m), 7.10-7.00 (2H, m), 4.63 (1H, s), 4.07 (2H, m), 2.74 (2H, m), 2.47 (2H, m), 1.76-1.22 (12H, bm), 1.08 (6H, m).

HPLC: RT = 14.16 min. (Beckman 235328 C-18 5 μm 4.6 mm × 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

-84-

Step (d): Preparation of 3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-*N*-hydroxybenzenecarboximidamide

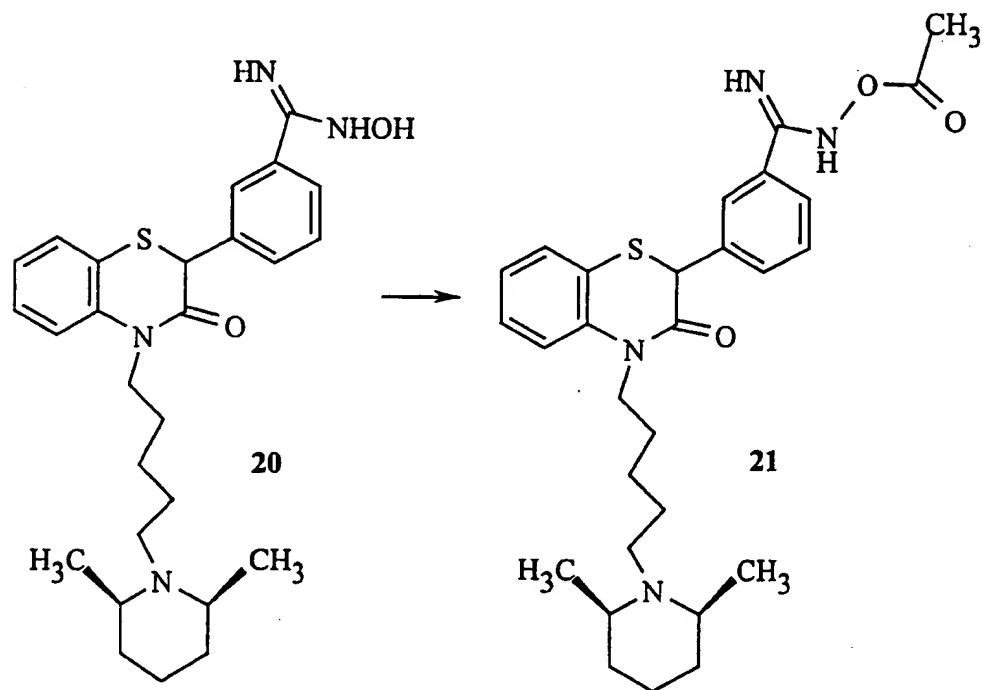


5 To (**19**) (0.30 g, 0.67 mmol) in methanol (10 mL) were added hydroxylamine hydrochloride (0.116 g, 1.67 mmol) and diisopropylethylamine (0.12 mL, 0.67 mmol). The solution was stirred at room temperature for 24 hours. The solvent was evaporated in vacuo, and the oil was dried under high vacuum to give (**20**) in quantitative yield.

10 HPLC: RT = 8.83 min. (Beckman 235328 C-18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

-85-

Step (e): Preparation of 3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-*N*-hydroxyacetatebenzenecarboximidamide

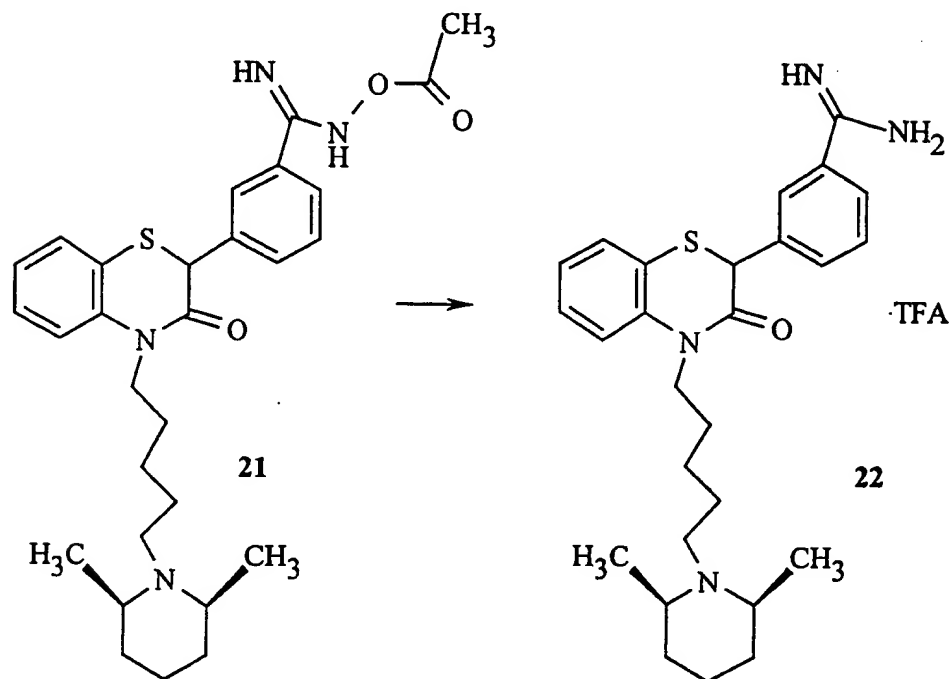


To (**20**) (0.32 g, 0.66 mmol) was added acetic anhydride (2 mL) and the solution was stirred at room temperature for 2 hours. The solution was diluted with acetic acid, and the solvent was evaporated in vacuo to give (**21**) as a yellow oil in quantitative yield.

HPLC: RT = 12.08 min. (Beckman 235328 C-18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nM).

-86-

Step (f): Preparation of 3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-benzenecarboximidamide



5 To (21) (0.34 g, 0.65 mmol) in acetic acid (2 mL) was added 20%
palladium on carbon (45 mg) and hydrogenated at 23°C for 2 hours. The mixture
was filtered through Celite and the filter pad washed with acetic acid. The
combined filtrate and washings were evaporated in vacuo, and purified by
10 preparative HPLC (Vydac 218TP1022 C-18, eluted with a mixture of solvents
consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic
acid in acetonitrile, gradient profile 95:5 (i):(ii) to 60:40 (i):(ii) over 90 minutes,
flow rate 20 mL/minute, $\lambda = 214$ nM) and lyophilized to give 50 mg (16%) of
product (22) as a fluffy off-white solid.

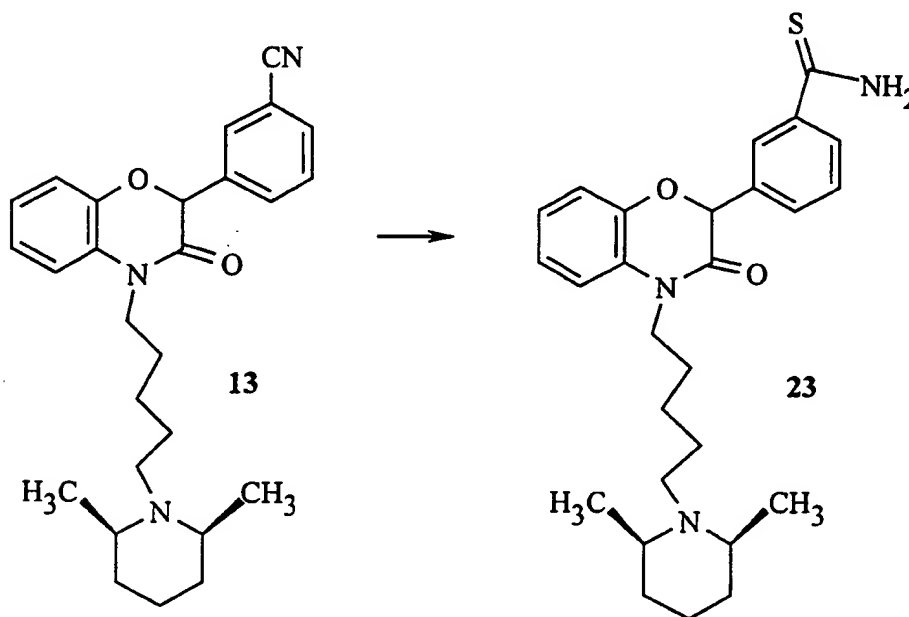
15 ^1H NMR (DMSO, 400 MHz): δ 9.33 (1H, s), 9.18 (1H, s), 7.69 (3H, m),
7.55 (1H, m), 7.41 (2H, m), 7.33 (1H, m), 7.07 (1H, m), 5.11 (1H, s), 4.09
(2H, m), 3.38 (2H, m), 3.24 (2H, m), 3.10 (2H, m), 2.91 (2H, m), 1.84 (2H, m),
1.66-1.33 (6H, bm), 1.24 (6H, m).
CI MS $M+1 = 465$, $M-1 = 464$.

-87-

HPLC: RT = 8.92 min. (86%) and 8.19 min. (13%). (Beckman 235328 C-18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

EXAMPLE 4

3-(4-5-[(2*R*,6*S*)-2,6-Dimethylhexahydro-1-pyridinyl]pentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-benzenecarbothioamide



In a three-necked flask, intermediate (13) (0.49 g, 1.14 mmol) was dissolved in pyridine (50 mL). Nitrogen was bubbled through the solution for 30 minutes. Hydrogen sulfide was bubbled through the yellow solution for 20 minutes. The solution turned green and the flask was sealed and stirred for 24 hours at room temperature. HPLC indicated that the reaction was complete. Nitrogen was bubbled through the solution for 30 minutes. The solution was evaporated in vacuo, coevaporated with toluene, and purified by preparative HPLC (Vydac 218TP1022 C-18, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in

-88-

acetonitrile, gradient profile 95:5 (i):(ii) to 60:40 (i):(ii) over 90 minutes, flow rate 20 mL/minute, $\lambda = 214$ nm) and lyophilized to give 28 mg (6%) of product (23) as a yellow solid.

¹H NMR (DMSO, 400 MHz): δ 9.92 (1H, s), 9.55 (1H, s), 7.97 (1H, s), 7.75 (1H, m), 7.48 (1H, m), 7.41 (1H, m), 7.25 (1H, m), 7.14-6.99 (3H, m), 5.91 (1H, s), 3.99 (2H, m), 3.37 (2H, bs), 3.24 (2H, bs), 3.11 (2H, m), 2.92 (2H, bs), 1.84 (2H, m), 1.70-1.38 (6H, m), 1.23 (6H, m).

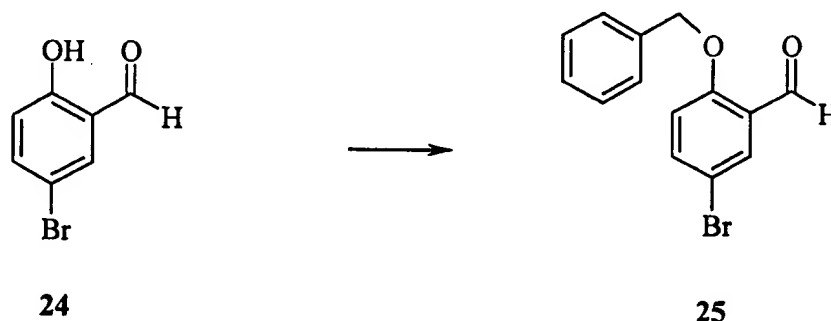
CI MS M+1 = 466.

HPLC: RT = 12.48 min. (Beckman 235328 C-18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, $\lambda = 214$ nm).

EXAMPLE 5

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide

Step (a): Preparation of 2-(benzyloxy)-5-bromobenzenecarbaldehyde

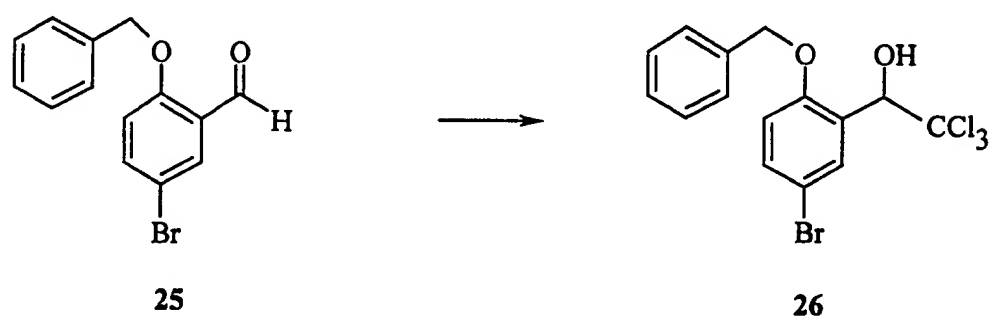


To 5-bromosalicylaldehyde (24) (10.01 g, 49.8 mmol) in DMF (50 mL) were added benzyl bromide (6.5 mL, 54.6 mmol) and potassium carbonate (13.76 g, 99.6 mmol). The reaction mixture was stirred at room temperature for 72 hours. The solution was diluted with water, and extracted with ethyl acetate (3 \times 200 mL). The combined organic extracts were washed with brine (2 \times 100 mL), dried with magnesium sulfate, filtered, evaporated in vacuo, and

dried under high vacuum. The product (**25**) was crystallized from ethyl acetate in hexane to give 10.96 g (76%) as a white solid.

¹H NMR (CDCl₃, 300M): δ 10.47(1H, s), 7.95(1H, m), 7.61(1H, m), 7.43-7.39(5H, m), 6.95(1H, m), 5.18(2H, s).

5 Step (b): Preparation of 1-[2-(benzyloxy)-5-bromophenyl]-2,2,2-trichloro-1-
ethanol

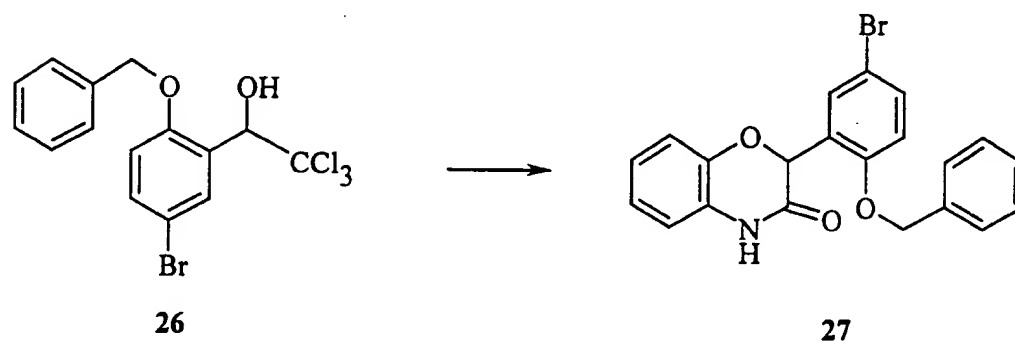


Into a mixture of lead(II) bromide (1.38 g, 3.76 mmol) and finely cut aluminum foil (1.02 g, 37.8 mmol) in DMF (188 mL) were added (25) (10.96 g, 37.6 mmol) and carbon tetrachloride (7.6 mL, 78.8 mmol), and the mixture was stirred at ambient temperature 3 hours. The reaction was quenched with aqueous 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were washed with brine (200 mL), dried with magnesium sulfate, filtered, evaporated in vacuo, and dried under high vacuum to give the trichloromethyl carbinol (26) as a brown oil in quantitative yield.

¹H NMR (CDCl₃, 300MHz): δ 7.82(1H, m), 7.46-7.37(6H, m), 6.87(1H, m), 5.71(1H, s), 5.11(2H, m), 3.85(1H, bs).

-90-

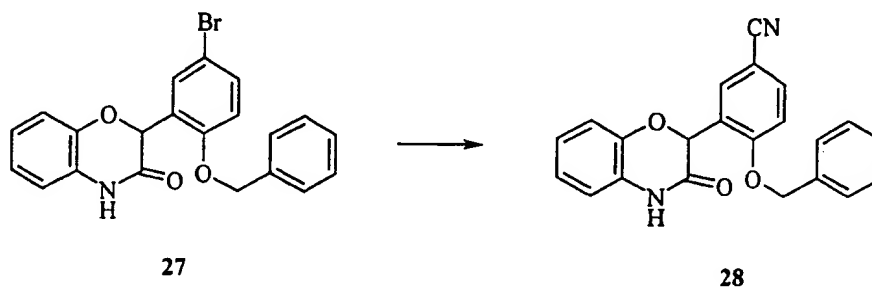
Step (c): Preparation of 2-[2-(benzyloxy)-5-bromophenyl]-2H-1,4-benzoxazin-3(4H)-one



To o-aminophenol hydrochloride (0.88 g, 6.04 mmol) in DMSO (15 mL) was added sodium hydride (1.21 g, 30.2 mmol). After bubbling and evolution of heat ceased, a solution of (26) (2.50 g, 6.09 mmol) in DMSO (10 mL) was added dropwise over 30 minutes at room temperature. After evolution of heat ceased, the mixture was stirred at 70°C for 4 hours. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate (5 × 500 mL). The combined organic extracts were washed with brine (200 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified on a silica gel column eluted with 20% ethyl acetate in hexane. The product (27) was isolated 0.67 g (27%) as a solid.

¹H NMR (CDCl₃, 300MHz): δ 7.91(1H, bs), 7.51(1H, m), 7.43(1H, m), 7.27(5H, m), 6.97-6.85(4H, m), 6.67(1H, m), 5.83(1H, s), 5.05(2H, m).

Step (d): Preparation of 4-(benzyloxy)-3-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarbonitrile

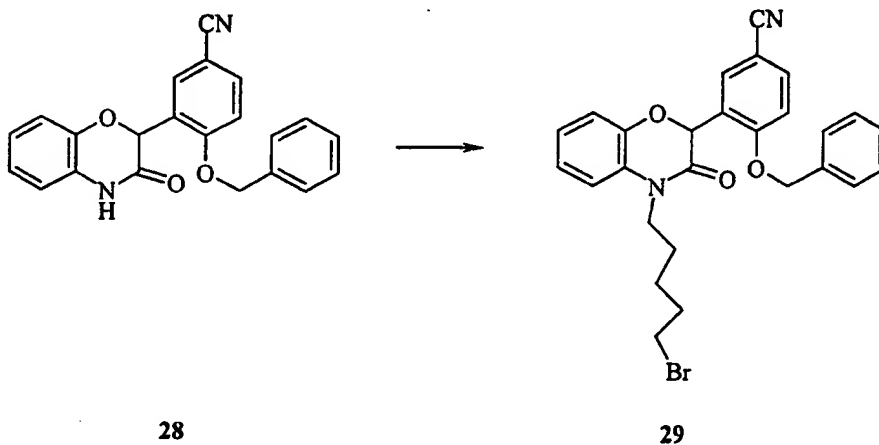


-91-

A mixture of the benzoxazinone (27) (0.17 g, 0.477 mmol) and cuprous cyanide (0.09 g, 1.00 mmol) in DMF (3 mL) was stirred at 160°C for 16 hours in a sealed tube. The solution was cooled, diluted with water (50 mL) and ammonium hydroxide (50 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried with magnesium sulfate, filtered, evaporated in vacuo, and dried under high vacuum to give 0.16 g (94%) of product (28) as a solid.

¹H NMR (CDCl₃, 300MHz): δ 9.82(1H, bs), 7.73-7.64(2H, m), 7.31(5H, m), 7.06-6.96(4H, m), 6.70(1H, m), 5.86(1H, s), 5.15(2H, m). CI MS M+1= 357 M-1=356.

Step (e): Preparation of 4-(benzyloxy)-3-[4-(5-bromopentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarbonitrile



To the benzoxazinone (28) (1.63 g, 4.57 mmol) in DMF (5 mL) was added sodium hydride (0.20 g, 5.00 mmol) and the solution was stirred at 0°C for 10 minutes until bubbling stopped. To this solution was added 1,5-dibromopentane (2.5 mL, 18.3 mmol) and the solution was stirred at 0°C for additional 2 hours. The solution was diluted with water, and extracted with ethyl acetate (5 × 200 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The

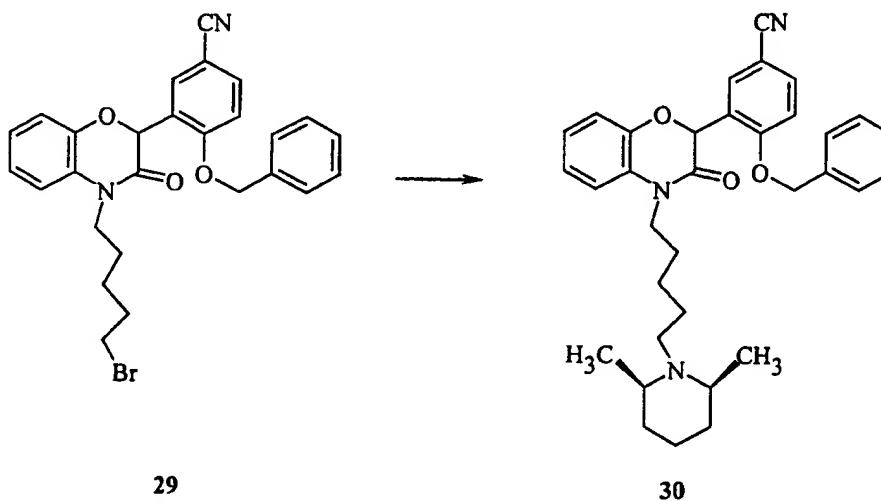
-92-

residue was purified on a silica gel column eluted with 20% ethyl acetate in hexane. The product (29) was isolated 1.14 g (61%) as a foam.

¹H NMR (CDCl₃, 300MHz): δ 7.63(2H, m), 7.31(5H, m), 7.07-6.94(5H, m), 5.83(1H, s), 5.14(2H, m), 3.89(2H, m), 3.37(2H, m), 1.86(2H, m), 1.55(4H, m).

5 CI MS M+1= 507/505 M-1=506/504.

Step (f): Preparation of 4-(benzyloxy)-3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarbonitrile



10 To (29) (1.14 g, 2.26 mmol) was added *cis*-2,6-dimethylpiperidine (10 mL, 74 mmol). The solution was stirred at 70°C for 16 hours. The solution was cooled, diluted with water, and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with saturated sodium bicarbonate (2 × 100 mL), washed with brine (2 × 100 mL), dried with magnesium sulfate, filtered,

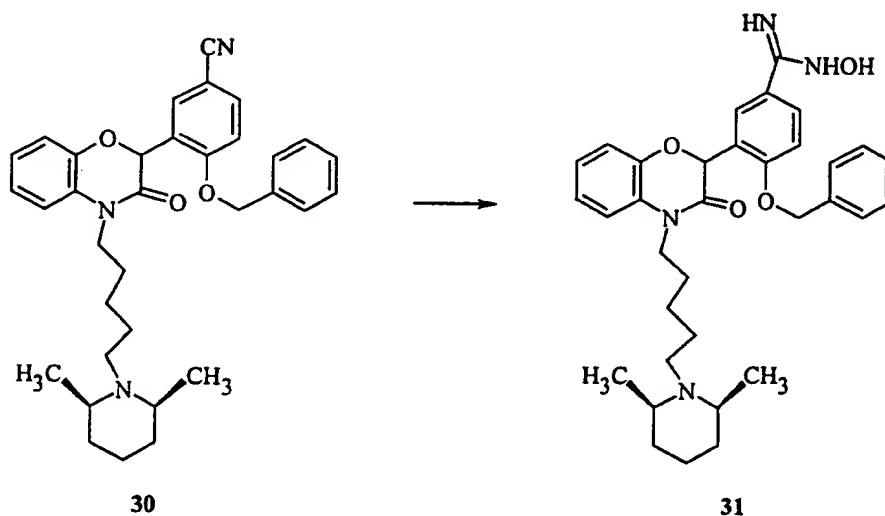
15 evaporated in vacuo, coevaporated with toluene, and dried under high vacuum to give (30) as a yellow oil in quantitative yield.

¹H NMR (CDCl₃, 300MHz): δ 7.56(2H, m), 7.25(5H, m), 7.10(1H, m), 7.00-6.89(4H, m), 5.78(1H, s), 5.09(2H, m), 3.80(2H, m), 2.64(2H, bs), 2.37(2H, bs), 1.59-1.15(12H, bm), 1.00(6H, m).

-93-

HPLC: RT = 16.26 minutes (Beckman 235328 C18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

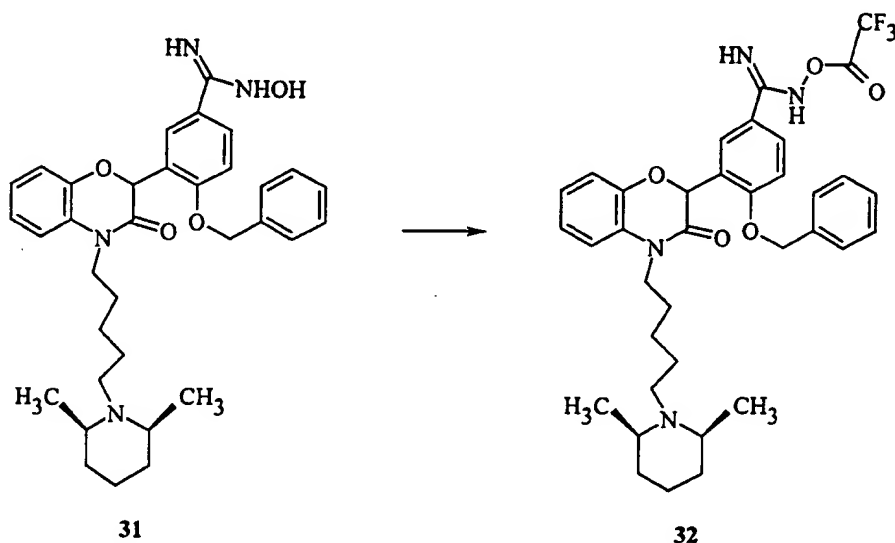
- 5 Step (g): Preparation of 4-(benzyloxy)-3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-hydroxybenzenecarboximidamide



- To (30) (1.21 g, 2.25 mmol) in methanol (25 mL) were added
 10 hydroxylamine hydrochloride (0.39 g, 5.61 mmol) and diisopropylethylamine (0.39 mL, 2.24 mmol). The solution was stirred at room temperature for 16 hours. The solvent was evaporated in vacuo and the oil was dried under high vacuum to give (31) in quantitative yield.
 HPLC: RT = 13.46 minutes (Beckman 235328 C18 5 μ m 4.6 mm \times 25 cm, eluted
 15 with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

-94-

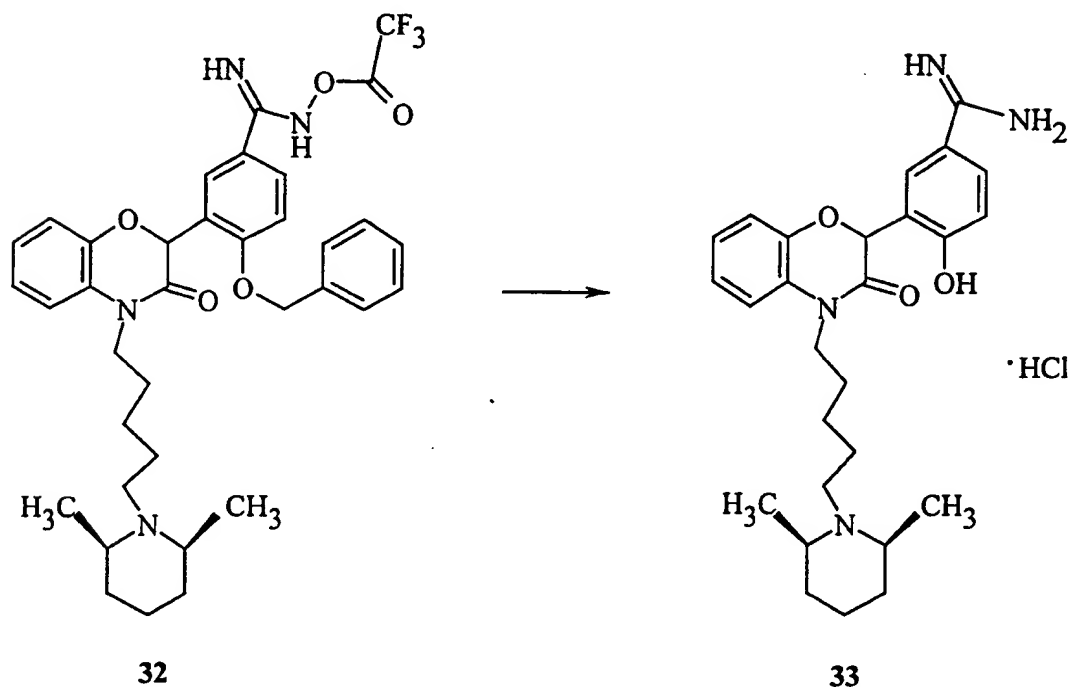
Step (h): Preparation of 4-(benzyloxy)-3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-[(2,2,2-trifluoroacetyl)oxy]benzenecarboximidamide



- 5 To **(31)** (1.28 g, 2.24 mmol) was added trifluoroacetic anhydride (10 mL) and the solution was stirred at room temperature for 2 hours. The solvent was removed in vacuo to give **(32)** as a yellow oil in quantitative yield.
- HPLC: RT = 21.62 minutes (Beckman 235328 C18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and
- 10 (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

-95-

Step (i): Preparation of 3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide



- 5 To (32) (0.149 g, 2.24 mmol) in trifluoroacetic acid (32 mL) was added 20% palladium on carbon (0.2 g) and hydrogenated at 23°C for 48 hours. The mixture was filtered and the filter pad washed with trifluoroacetic acid. The combined filtrate and washings were evaporated in vacuo, and the residue was purified by preparative HPLC (Vydac 218TP54 C18, eluted with a mixture of
- 10 solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 95:5 (i):(ii) to 60:40 (i):(ii) over 90 minutes, flow rate 20 mL/minute, $\lambda = 214$ nm) and lyophilized to afford a white powder. To the white powder in acetonitrile (2 mL) and water (200 mL) was added Amberlite® IRA-400(Cl) ion exchange resin. The mixture was filtered,
- 15 and the filtrate was lyophilized to give 553 mg (45%) of (33) as a white solid.
- ^1H NMR (DMSO, 300MHz): δ 11.22(1H, s), 9.16(1H, s), 8.86(2H, s), 7.74(2H, m), 7.25(1H, m), 7.11-6.95(4H, m), 5.78(1H, s), 4.06-3.93(2H, m), 3.17(2H, m), 3.05(2H, m), 1.79-1.37(12H, m), 1.23(6H, m).

-96-

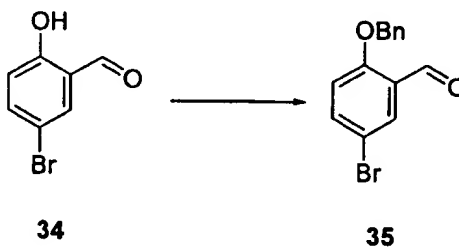
CI MS M+1 = 465

HPLC: RT = 8.22 (Beckman 235328 C18 5 μ m 4.6 mm \times 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) 0.1% trifluoroacetic acid in acetonitrile, gradient profile 80:20 (i):(ii) to 10:90 (i):(ii) over 23 minutes, flow rate 1.5 mL/minute, λ = 214 nm).

Example 6

3-((2*S*)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide

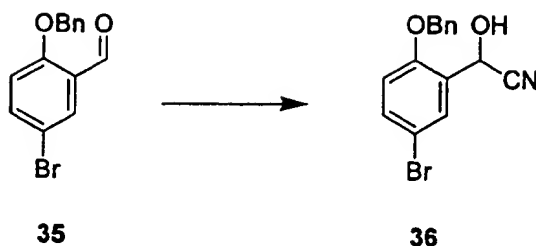
Step (a): Preparation of 2-(benzyloxy)-5-bromobenzenecarbaldehyde



5-bromosalicylaldehyde (**34**) (50.0g, 0.249 moles) was suspended in 150ml EtOH with stirring. KOH (13.97g, 0.249 moles) was dissolved in 40ml water and added to the aldehyde suspension. After 30 minutes benzyl bromide (51.05g, 35.5ml, 0.298 moles) was added slowly. The mixture was refluxed overnight. After cooling to room temperature water (50 mL) was added and then after 5 minutes an off white solid was collected by filtration. This was dried overnight in vacuum to afford 61.71g of the desired product (**35**), 84.6% yield. ¹H NMR (CDCl₃) δ 10.46 (1H, s), 7.94 (1H, d), 7.60 (1H, dd), 7.41 (5H, m), 6.95 (1H, d), 5.18 (2H, s). APCI MS: No M+1, M-91 (201). HPLC: 20.91 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.)

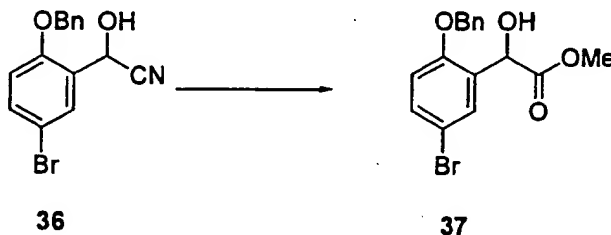
Step (b): Preparation of 2-[2-(benzyloxy)-5-bromophenyl]-2-hydroxyacetonitrile

-97-



To a suspension of (35) (50g, 0.172 moles) in MeOH (400 mL) was added KCN (50.31g, 0.773 moles) which generated a yellow color. Acetic acid (15.72ml, 0.275 moles) was added dropwise over 10 minutes, and the reaction stirred at room temp. for 2.5 hours. The mixture was filtered and concentrated by 75%. Ethyl acetate (250 mL) was added and then after washing with water (2x150 ml), sat. NaCl (1x150 ml), the organic phase was dried over MgSO₄, and finally concentrated to a brown oil. Chromatographed on flash silica using 10%→20% ethyl acetate in hexane affords (36) 35.4g desired product, 64.8% yield. (1H NMR CDCl₃) δ 7.58 (1H, d), 7.35-7.50 (6H, m), 6.95 (1H, d), 5.55 (1H, d), 5.18 (2H, s), 3.30 (1H, d). APCI MS No M+1, M-91 (201): HPLC: 18.04 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)→90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0→22 min.)

Step (c): Preparation of methyl 2-[2-(benzyloxy)-5-bromophenyl]-2-hydroxyacetate

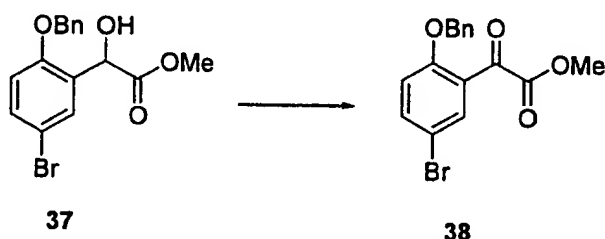


Diethyl ether (45 mL), dioxane (45 mL), MeOH (12 mL) were mixed at room temp. and then HCL gas was bubbled into the solution for 3-4 minutes at a good rate (to make a saturated HCl solution). The HCl solution was added to the (36) (35.2g, 0.111 moles), which after 15 minutes caused a thick white ppt to form.

-98-

After an additional 45 minutes of stirring the white solid was filtered and washed with diethyl ether (3x100ml). This solid was then stirred into 200ml of 1:1 dioxane:water, and allowed to stir until the mixture became homogenous, approx. 1 hour. Water (100 mL) was added and the solution was extracted with ethyl acetate (2x200ml). The organic layer was dried over MgSO₄, evaporated to afford a clear oil, which afforded (37) as a waxy white solid after drying overnight under high (31.3 g, 80.4%). (1H NMR CDCl₃) δ 7.42 (1H, d), 7.3-7.4 (6H, m) 6.80 (1H, d), 5.32 (1H, bd), 5.10 (2H, dd), 3.7 (3H, s), 3.6 (1H, bd). APCI MS M+23, No M+1. HPLC: 17.43 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA) --> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.)

Step (d): Preparation of methyl 2-[2-(benzyloxy)-5-bromophenyl]-2-oxoacetate



15

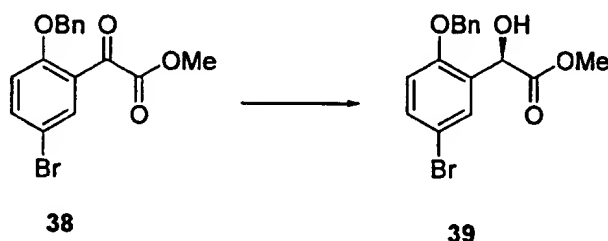
Methylene chloride (30 mL) was cooled to minus70 °C under N₂ with stirring via dry ice/acetone bath, and then oxalyl chloride (3.07ml, 0.035 moles) was added. DMSO (4.97ml, 0.70 moles) was then added as a 1:1 mix with CH₂Cl₂ slowly down the side of the flask, not allowing the temperature to go above -60 °C. This was stirred for 15 minutes, and then the alcohol (37) (10.26g, 0.026 moles) was added as a solution in CH₂Cl₂, dropwise, again not allowing the temp. to climb above -60 °C. This mixture was stirred at -65 °C for 30 minutes, then added Et₃N (20.40ml, 0.145 moles) dropwise, not allowing temp. to reach -60 °C. Upon warming to room temp., water (150 ml) was added and the product was extracted into ethylacetate. The organic phase was dried over MgSO₄, and then rotovaped to a pale yellow solid, (38) 10.03g, 98% yield. (1H NMR CDCl₃) δ 7.99 (1H, d), 7.65 (1H, dd), 7.38-7.42 (5H, m), 6.96 (1H, d), 5.05 (2H, s), 3.35 (3H, s). APCI MS No M+1, M-91 (257). HPLC: 20.95 min. on C-18 column @ 1.5 ml/min. 20%

25

-99-

CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.)

5 Step (e): Preparation of methyl (2*R*)-2-[2-(benzyloxy)-5-bromophenyl]-2-hydroxyethanoate



10 The ketoester (**38**) (12.9g, 0.037 moles) was slurried in CH₂Cl₂ (6 mL), then R-Alpine Borane (14.07ml, 0.052moles) was added dropwise and the slurry allowed to stir at room temp. After 5 days an additional amount of R-Alpine Borane (10.1ml, 0.037moles) was added and the mixture was stirred for another 24 hours. Acetaldehyde (6.0ml) was added together with CH₂Cl₂ (100ml) and ethanolamine

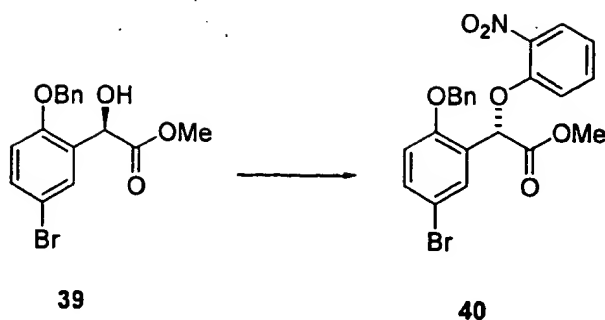
15 (4.0ml), and then the mixture was stirred for 1 hour. The mixture was evaporated by ~50% and then columned directly on flash silica using 15-->20% ethyl acetate in hexane to afford the desired product (**39**), 12.2g 94% yield. (1H NMR CDCl₃) δ 7.42 (1H, d), 7.3-7.4 (6H, m) 6.80 (1H, d), 5.32 (1H, bd), 5.10 (2H, dd), 3.7(3H, s), 3.6 (1H, bd). APCI MS M+23, No M+1. HPLC: 17.43 min. on C-18 column @

20 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.) Chiral HPLC 8.07 min. (95%ee) @ 2.0 ml/min. 20% EtOH (.1% TEA) in Hexane on (Phenomenex) Chirex (R)-NGLY and DNB chiral column.

25

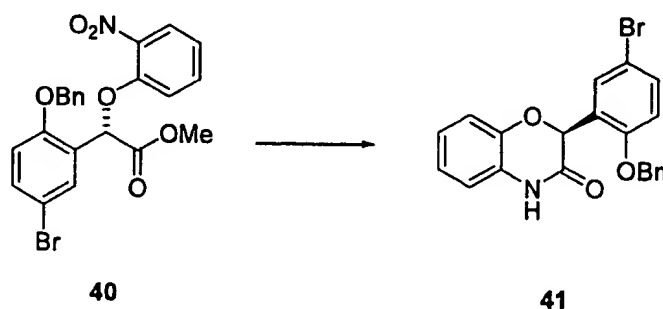
Step (f): Preparation of methyl (2*S*)-2-[2-(benzyloxy)-5-bromophenyl]-2-(2-nitrophenoxy)ethanoate

-100-



The chiral alcohol (39) (5.0g, 0.014 moles) was dissolved in ethyl acetate (75 mL), then triphenyl phosphine (4.85g, 0.018 moles) and o-nitro phenol (2.37g, 0.017 moles) were added with stirring. The reaction was put under N₂ and cooled to -40 °C via dry ice/acetone bath, and the DIAD (3.63ml, 0.018 moles) was added dropwise. The reaction stirred at -40 °C for 2 hours. The volume was reduced by ~50% and the reaction was chromatographed on flash silica using 15%→ 20% ethyl acetate in hexane to afford desired product (40) (5.6g, 83.3%). (1H NMR CDCl₃) δ 7.85 (1H, dd), 7.71 (1H, d), 7.3-7.45 (6H, m), 7.07 (1H, t), 7.0 (1H, d), 6.85 (1H, d), 6.20 (1H, s), 5.12 (2H, dd), 3.72 (3H, s). HPLC: 22.07 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)→ 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0→22 min.) No separation of enantiomers on chiral HPLC.

Step (g): Preparation of (2*S*)-2-[2-(benzyloxy)-5-bromophenyl]-2*H*-1,4-benzoxazin-3(4*H*)-one

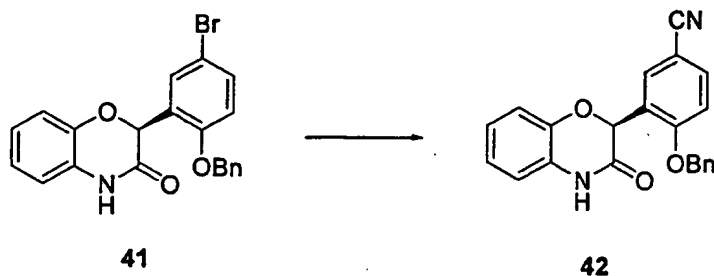


The chiral ether (40) (9.3g, 0.020 moles) was dissolved in 400ml MeOH and then 10g of neutral RaNi was added (washed with water 10x, then MeOH 3x). The

-101-

mixture was placed under H₂ at 53.8psi. A pressure drop to 48.0 psi after 15 hrs was noted. The reaction was filtered and evaporated which after chromatography, on flash silica using 20% ethyl acetate in hexane, afforded the desired product (41) (5.17g, 64%, and 92.8% ee via chiral HPLC). Variable results were obtained on attempts to improve the enantiomeric excess by recrystallisation from EtOAc. The filtrate typically contained material of enriched enantiomeric excess. Thus material was ultimately obtained of 95.5%ee. (1H NMR CDCl₃) δ 8.2 (1H, bs), 7.52 (1H, d), 7.42 (1H, dd), 7.33-7.42 (5H, m), 6.82-6.98 (4H, m), 6.68 (1H, d), 5.82 (1H, s) 5.02 (1H, dd) APCI MS M+1 (411). HPLC: 17.48 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA) → 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0 → 22 min.). Chiral HPLC 6.12 min. (95.5%ee) @ 2.0 ml/min. 20% EtOH (.1% TEA) in Hexane on (Phenomenex) Chirex (R)-NGLY and DNB chiral column.

Step (h): Preparation of 4-(benzyloxy)-3-[(2*S*)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarbonitrile



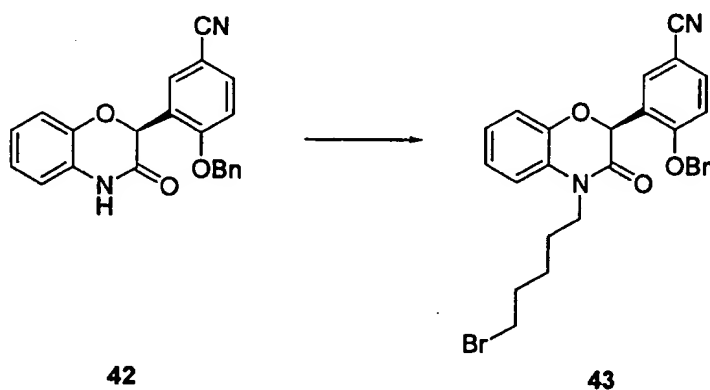
To (41) (4.15g, 0.010moles) in DMF (6 mL) was added CuCN (1.57g, 0.18 moles) and the mixture heated to 160 °C with stirring under N₂ overnight. The reaction mixture was cooled to R.T. and then ethyl acetate (100 mL) was added. Washing with sat. brine/NH₄OH (9:1) (2x130 ml), drying over MgSO₄, and then evaporation afforded a brown solid. A portion was crystallised from ethylacetate to afford (0.76g) and the remainder was purified by chromatography 25% → 50% ethyl acetate in hexane to afford another 1.53g, (2.29g, 63.6%). (1H NMR CDCl₃) δ 8.26 (1H, bs), 7.72 (1H, d), 7.65 (1H dd), 7.30 (5H, s), 7.03 (1H, d), 6.91-6.98 (3H, m), 6.72 (1H, dd), 5.86 (1H, s), 5.14 (2H, dd). APCI MS M+1

-102-

(357). HPLC: 17.80 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.)
Chiral HPLC 6.51 min. @ 2.0 ml/min. 20% EtOH (.1% TEA) in Hexane on (Phenomenex) Chirex (R)-NGLY and DNB chiral column.

5

Step (i): Preparation of 4-(benzyloxy)-3-[(2*S*)-4-(5-bromopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarbonitrile



10

To (**42**) (2.2g, 0.0062 moles) in dry DMF (15 mL) under N₂ with stirring was added dibromopentane (3.76ml, 0.025 moles) and then the mixture was cooled too 0 °C. KN(TMS)₂ (11.11ml 0.5M sol., .0055 moles) was added dropwise over ~15 minutes and the mixture was stirred for 1h at 0 °C. , then at room temp for 2 hrs. Ethyl acetate (75mL) was added and the mixture extracted with water (2x50ml), dried the organic layer over MgSO₄ and rotovaped off solvent. Chromatography on flash silica to get afforded the required product (**43**) (1.51g, 48%). (1H NMR CDCl₃) δ 7.65 (2H, d), 7.31 (5H, s), 6.94-7.07 (5H, m), 5.82 (1H, s), 5.14 (2H, dd), 3.89 (2H, dd), 3.37 (2H, t), 1.87 (2H, m), 1.58 (2H, m), 1.50 (2H, m.). APCI MS M+1 (505). HPLC: 23.01 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.)

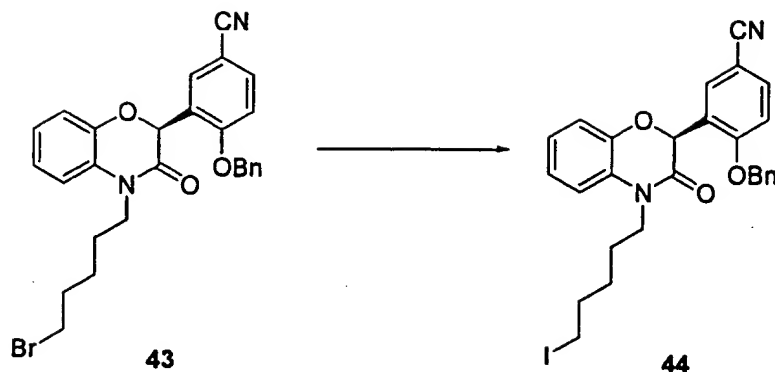
15

20

25

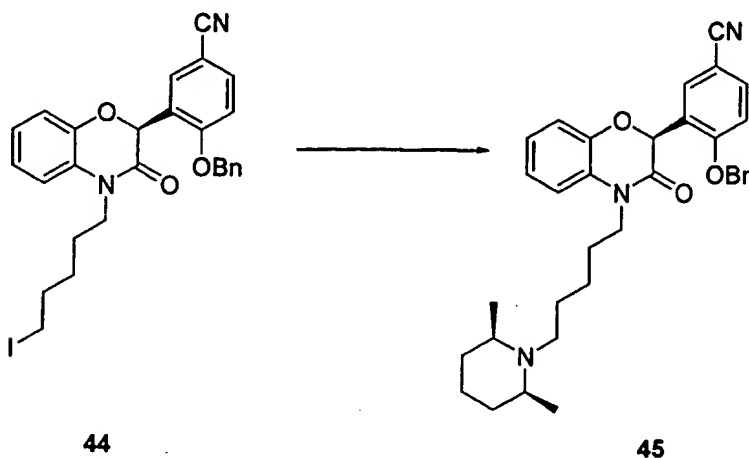
Step (j): Preparation of 4-(benzyloxy)-3-[(2*S*)-4-(5-iodopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]benzenecarbonitrile

-103-



To (43) (1.49g, 0.0029 moles) in acetone (20 ml) and added the NaI (2.21g, 0.015
 5 moles) and then the mixture was refluxed for 1 hour, filtered, rotovaped off
 acetone, slurried up in 30ml ethyl acetate and washed with 30ml H₂O, then 30ml
 sat NaCl, dried the organic layer over MgSO₄ and rotovaped to a yellow oil (44),
 1.48g crude. (1H NMR CDCl₃) δ 7.63 (2H, d), 7.31 (5H, s), 6.93-7.10 (5H, m),
 5.81 (1H, s), 5.15 (2H, dd), 3.88 (2H, t), 3.15 (2H, t), 1.82 (2H, m), 1.60 (2H, m),
 10 1.45 (2H, m). APCI MS M+1 (553). HPLC: 23.54 min. on C-18 column @ 1.5
 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in
 H₂O(.1% TFA) (0--->22 min.)

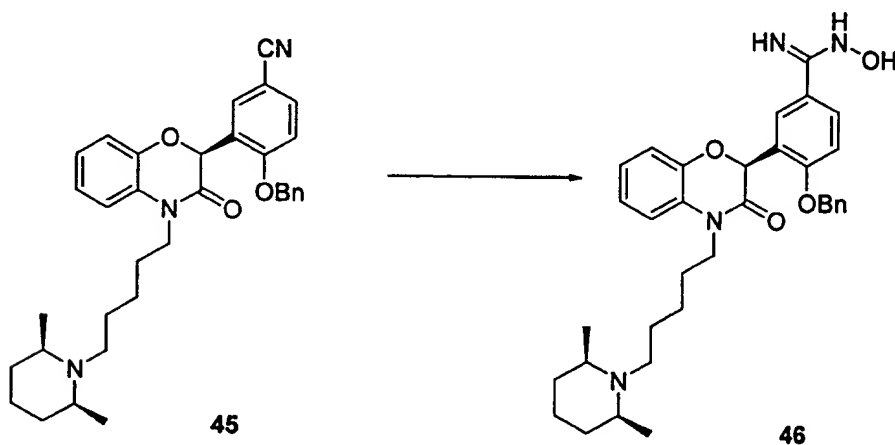
Step (k): Preparation of 4-(benzyloxy)-3-((2S)-4-5-[(2R,6S)-2,6-
 15 dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-
 benzoxazin-2-yl)benzenecarbonitrile



-104-

To (44) in dry DMF (2 mL) was added cis-2,6 dimethylpiperidine (2 mL) and the mixture stirred at room temp. overnight. Added 30ml ethyl acetate and washed with H₂O (2x30ml), dried the organic layer over MgSO₄ and rotovaped to a pale yellow oil, 1.27g, 80.4% yield over 2 steps. Used without purification in next reaction. (1H NMR) δ 7.61-7.64 (2H, m), 7.31 (5H, s), 6.95-7.06 (5H, m), 5.84 (1H, s), 5.14 (2H, m), 3.88 (2H, m), 2.68-2.73 (2H, m), 2.43 (2H, m), 1.21-1.76 (12H, m), 1.04-1.10 (6H, m) APCI MS M+1 (538). HPLC: 14.95 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.)

Step (1): Preparation of 4-(benzyloxy)-3-((2*S*)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-hydroxybenzenecarboximidamide



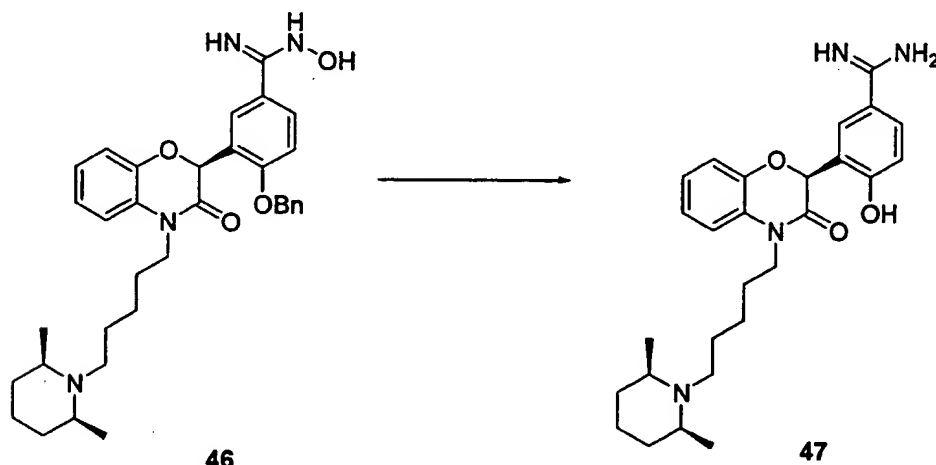
To (45) (0.54g, .001 moles) in 5ml MeOH was added hydroxylamine HCl (0.208g, 0.003 moles), then diisopropylethylamine (0.348ml, 0.002 moles) was added dropwise and the reaction stirred overnight at room temp. Rotovaped off MeOH, added 50ml CH₂Cl₂ and washed with sat. NaHCO₃, dried the organic layer over MgSO₄ and rotovaped to a white waxy solid (46), .560mg crude. Used without purification in next reaction. (1H NMR) δ 7.46-7.53 (2H, m), 7.20-7.27 (5H, m), 6.85-6.94 (5H, m), 5.85 (1H, s), 5.03 (2H, s), 3.87-3.95 (1H, m), 3.71-

-105-

3.78 (1H, m), 2.71-2.74 (2H, m), 2.47 (2H, bm), 1.19-1.64 (12H, m), 0.98-1.09 (6H, m). APCI MS M+1 (571). HPLC: 11.14 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.)

5

Step (m): Preparation of 3-((2*S*)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide



10

To (46) (0.50g, 0.00087 moles) in TFA (2 mL) was added 4ml TFAA (4 mL) and the mixture stirred at room temperature, under N₂, overnight. Rotovaped off the solvent to get a gray oil. Added TFA (5 mL), then added 0.060g 20% Pd/C, evacuated the flask, filled with H₂ (via balloon), repeated, and let stir under an atmosphere of H₂ overnight. Filtered the reaction through celite, washed with CH₂Cl₂ then rotovaped off the solvent. Chromatographed on prep HPLC.

15

Converted the clean fractions to the HCl salt by running through IRA 400(Cl) resin as an aqueous solution. Lyophilized to get 0.060g desired product (47). (1H NMR_{D₂O}) δ 7.60-7.65 (2H, m,), 7.18 (1H, d), 6.97-7.07 (3H, m), 6.90 (1H, d), 5.70 (1H, s), 4.07-4.12 (1H, m), 3.80-3.85 (1H, m), 1.24-1.77 (12H, m), 1.07-1.14 (6H, m). APCI MS M+1 (465). HPLC: 8.31 min. on C-18 column @ 1.5 ml/min. 20% CH₃CN(.1% TFA) in H₂O(.1% TFA)--> 90% CH₃CN(.1% TFA) in H₂O(.1% TFA) (0--->22 min.) Chiral HPLC 11.10 min. (90% ee) @ 1.0 ml/min.

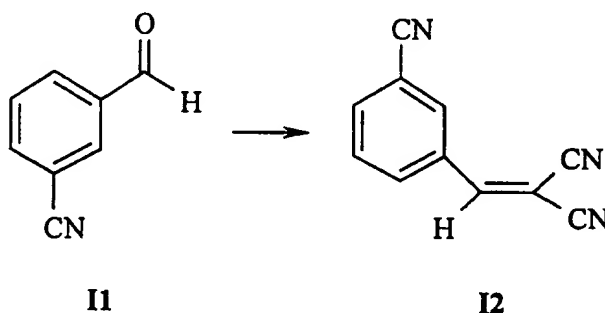
20

-106-

20% EtOH, 20% MeOH(.1mM NH₄Ac), 60% hexane on (Phenomenex) Chirex
(R)-NGLY and DNB chiral column.

5

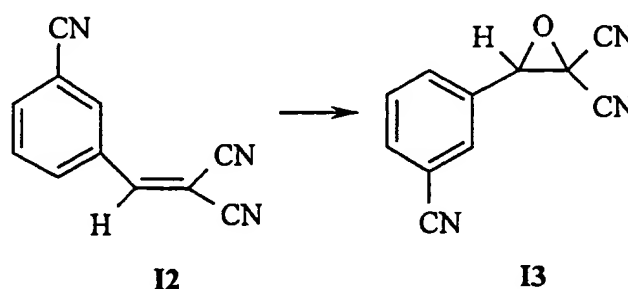
Intermediates

2-(3-Cyanophenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-oneStep (a): Preparation of 2-[(3-cyanophenyl)methylene]malononitrile

10 Into a mixture of 3-cyanobenzaldehyde (**I1**) (24.8 g, 0.189 mol) and
malononitrile (11.9 mL, 0.189 mol) in dioxane (120 mL) was added piperidine
(1.5 mL) slowly. The solution was stirred at room temperature for 1 hour. The
precipitate was filtered, washed with water, and dried in the high vacuum oven to
give 7.11 g (21%) of product (**I2**) as yellow solid. To the filtrate was added
ethanol and water and 10.29 g (30%) of additional product crystallized as yellow
15 solid.

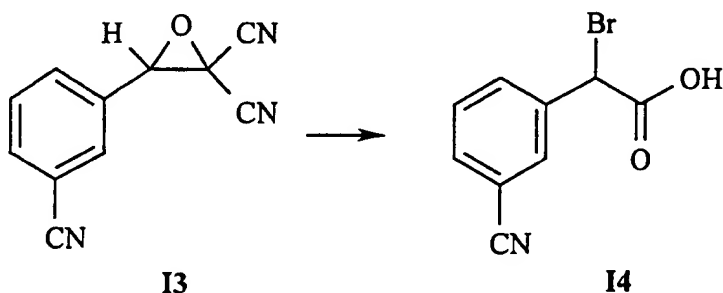
¹H NMR (CDCl₃, 300 MHz): δ 8.17 (1H, m), 8.51 (1H, m), 7.87 (2H, m),
7.68 (1H, m).

-107-

Step (b): Preparation of 3-(3-Cyanophenyl)-2,2-oxiranedicarbonitrile

In a three-necked flask, intermediate (**12**) (17.38 g, 97.0 mmol) was dissolved in acetonitrile (90 mL) and THF (113 mL) at room temperature with vigorous stirring. Sodium hypochlorite (183 mL) was added dropwise, while the pH of the solution was maintained between 4.5 and 6 throughout the addition by adding 2N sulfuric acid (20 mL). Once the addition was complete, stirring was continued for 20 minutes. Ethyl acetate was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The residue was flushed through a pad of silica gel eluting with 50% ethyl acetate in hexane. The product (**13**) was isolated 11.18 g (58%) as a tan solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.83 (1H, m), 7.76 (1H, m), 7.67 (2H, m), 4.78 (1H, s).

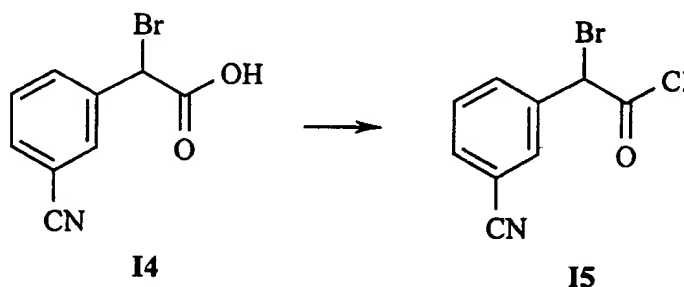
Step (c): Preparation of 2-Bromo-2-(3-cyanophenyl)acetic acid

-108-

To the epoxide (**I3**) (5.12 g, 26.2 mmol) in THF (30 mL) was added 48% HBr (4.4 mL), and the solution was refluxed for 3 hours. The THF was removed in vacuo, and the residue was dissolved in ether (200 mL). The acid is extracted from ether with 1N NaOH (100 mL). The aqueous solution was then acidified with HCl, and the acid is extracted with ether (2 × 200 mL). The combined organic phases were dried over magnesium sulfate, filtered, evaporated in vacuo, and dried under high vacuum to give 4.32 g (69%) of (**I4**) as a brown oil.

¹H NMR (CDCl₃, 300 MHz): δ 7.83 (1H, m), 7.73 (1H, m), 7.55 (1H, m), 7.41 (1H, m), 5.26 (1H, s).

10 Step (d): Preparation of 2-Bromo-2-(3-cyanophenyl)acetyl chloride

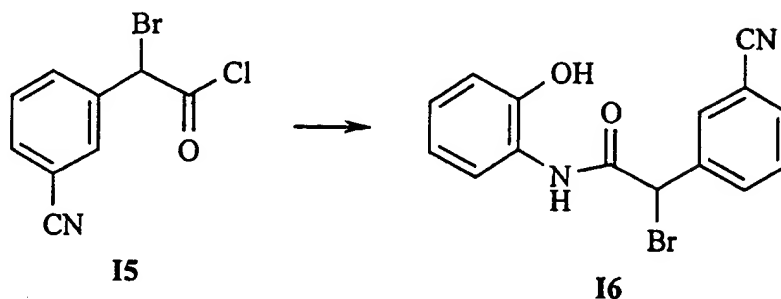


To the acid (**I4**) (1.01 g, 4.21 mmol) in dichloromethane (12 mL) were added oxalyl chloride (1 equiv.) and a catalytic amount of DMF (0.1 mL). Bubbling occurred and the resulting solution was stirred for 1 hour. The solvent was removed in vacuo to give (**I5**) in quantitative yield as a brown oil.

¹H NMR (CDCl₃, 300 MHz): δ 7.80-7.72 (3H, m), 7.592 (1H, m), 5.64 (1H, s).

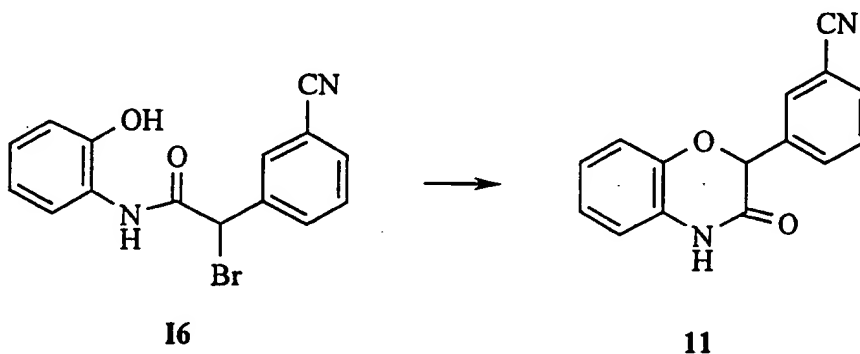
-109-

Step (e): Preparation of *N*l-(2-Hydroxyphenyl)-2-bromo-2-(3-cyanophenyl)acetamide



To (**15**) (1.08 g, 4.17 mmol) in dichloromethane (10 mL) were added
 5 o-aminophenol hydrochloride (0.62 g, 4.26 mmol) and diisopropylethylamine
 (0.72 mL, 4.11 mmol). The solution was stirred at room temperature for 4 hours.
 The solution was diluted with water and extracted with ethyl acetate (5 × 100
 mL). The combined organic extracts were washed with brine (200 mL), dried with
 magnesium sulfate, filtered, and evaporated in vacuo to give (**16**) in quantitative
 10 yield as a brown oil.

Step (f): Preparation of 2-(3-Cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one



To the benzoxazinone (**16**) (1.38 g, 4.17 mmol) in DMF (5 mL) was added
 potassium carbonate (1.40 g, 10.1 mmol), and the solution was stirred at room
 15 temperature for 1 hour. The solution was diluted with water and extracted with
 ethyl acetate (3 × 150 mL). The combined organic extracts were washed with
 brine (2 × 100 mL), dried with magnesium sulfate, filtered, and evaporated

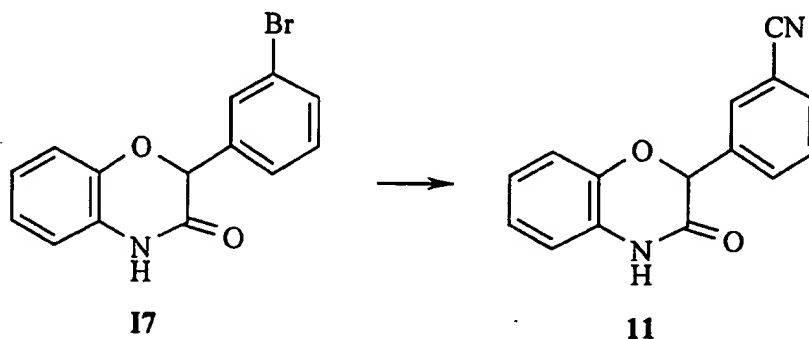
-110-

in vacuo. The residue was purified on a silica gel column eluted with 25% ethyl acetate in dichloromethane. The product (11) was isolated 0.48 g (46%) as a light orange solid.

^1H NMR (CDCl_3 , 300 MHz): δ 7.99 (1H, s), 7.75 (2H, m), 7.64 (1H, m), 7.49 (1H, m), 7.11-6.97 (3H, m), 6.80 (1H, m), 5.69 (1H, s).

Alternative procedure for preparation of 2-(3-Cyanophenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one

In a similar manner to steps (a) through (f) described above, but starting from 3-bromobenzaldehyde, 2-(3-bromophenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one may be prepared.



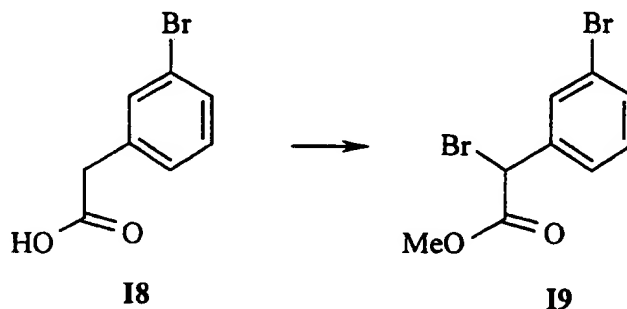
To a solution of 2-(3-bromophenyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one (17) (3.00 g, 9.87 mmol) in DMF (20 mL) was added Zinc cyanide (0.68 g, 5.79 mmol) and then tetrakis(triphenylphosphine) palladium (0) (0.96 g, 8 mol%). The degassed solution was heated at 100°C for 5 hours, cooled to room temperature, and then treated with water (50 mL). The product was extracted into ethyl acetate (2 × 100 mL), washed with brine (50 mL), dried over MgSO_4 , and then purified by silica gel chromatography, eluant 50% ethyl acetate in hexane. This process affords the title compound (1.866 g, 76%) that was recrystallized from ethanol/water. (APCI MS) 251.

-111-

Analysis $C_{15}H_{10}N_2O_2$:

Required: C, 71.99; H, 4.03; N, 11.19.

Found: C, 71.59; H, 4.22; N, 10.96.

Procedure for preparing methyl 2-bromo-2-(3-bromophenyl)acetate:

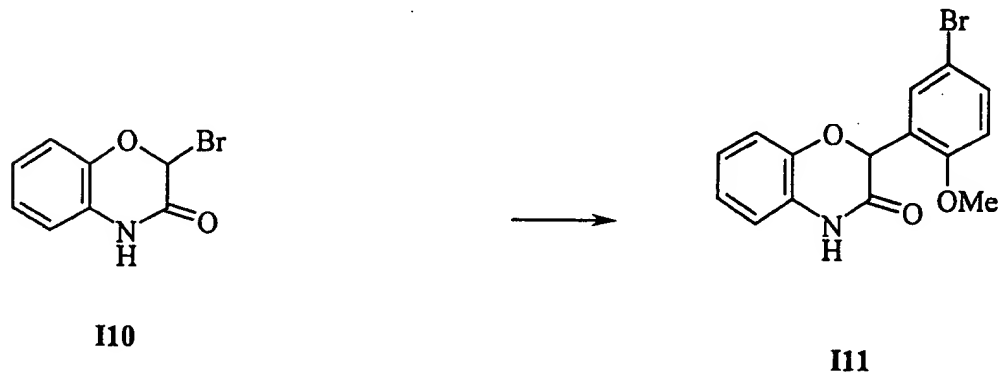
5

To 3-bromophenylacetic acid (10 g, 47 mmol) under argon was added PBr_3 (11.2 mL, 118 mmol) and the suspension stirred at room temperature for 45 minutes. Bromine (11.1 mL, 216 mmol) was added dropwise over 5 minutes. The mixture was stirred at $100^\circ C$ for 3 hours and then cooled. Anhydrous

10 methanol (35 mL) was added dropwise over 30 minutes, and then the reaction mixture was diluted with ether (400 mL), washed with 5% $NaHCO_3$ (800 mL), brine (200 mL), and then dried over $MgSO_4$. The mixture was filtered and concentrated in vacuo to afford material of sufficient purity to use directly.

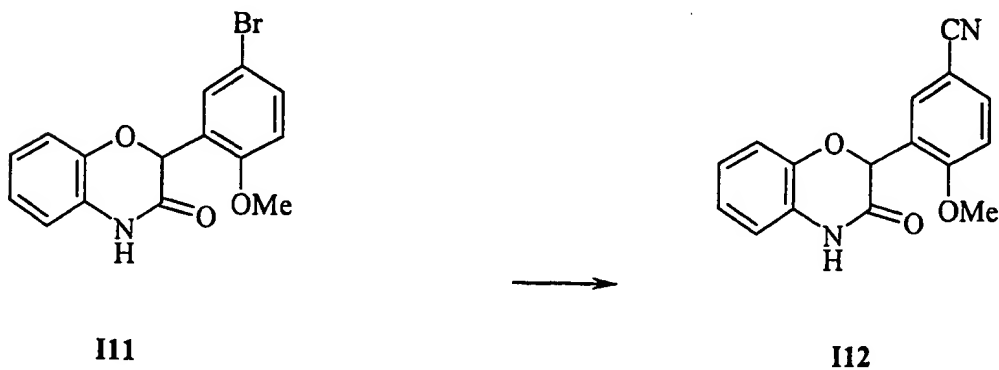
-112-

Alternative procedure for preparing 2-(5-bromo-2-methoxyphenyl)-2H-1,4-benzoxazin-3(4H)-one:



To 2-bromo-2H-1,4-benzoxazin-3(4H)-one (**I10**) (1.40 g, 6.14 mmoles) in methylene chloride (20 mL) was added 4-bromoanisole and then tin (IV) chloride. Addition of tin (IV) chloride caused a brown solution to form. The solution was refluxed for 5 hours, diluted with methylene chloride (100 mL) and washed with water (2 × 50 mL). After drying over Magnesium sulphate the mixture was concentrated until the product (**I11**) precipitated (0.58 g). Concentration of the mother liquors and chromatography on silica gel afforded an additional amount of product (**I11**) (0.55 g). (APCI MS) 334

Preparation of 4-methoxy-3-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarbonitrile



-113-

To a solution of 2-(5-bromo-2-methoxyphenyl)-2*H*-1,4-benzoxazin-3(4*H*)-one (I11) (0.90 g, 2.70 mmoles) in DMF (10 mL) was added copper (I) cyanide (1.3 g, 5 equiv.) and the mixture heated at 160°C for 12 hours. The mixture was cooled and methylene chloride (100 mL) and aqueous ammonium hydroxide (10 mL) were added. The methylene chloride layer was separated and dried over MgSO₄ which afforded the required product (I12) (0.67 g, 89%) upon evaporation in vacuo.

(APCI MS) 281

The invention compounds have demonstrated factor Xa, thrombin, and factor VIIa inhibitory activity in the standard assays commonly employed by those skilled in the art.

Determination of Factor Xa IC₅₀ and K_i Constants

The ability of compounds to act as inhibitors of human factor Xa catalytic activity is assessed by determination of that concentration of test substance that inhibits by 50% (IC₅₀) the ability of human factor Xa to cleave the chromogenic substrate S2765 (N-CBz-D-Arg-L-Gly-L-Arg-p-nitroanilide. 2HCl, DiaPharma). Typically, 145 µL human factor Xa (1 nM final, Enzyme Research Laboratories) in 10 mM HEPES, 150 mM NaCl, 0.1% BSA, pH 7.4 (HBSA buffer), and 5 µL of test substance in DMSO (2% final) are incubated for 60 minutes at room temperature. Following preheating to 37°C for 5 minutes, to this mixture is added 100 µL of S2765 (400 µM final) in HBSA buffer. The velocity of S2765 hydrolysis is determined at 37°C by measuring the initial rate of change of the optical density at OD₄₀₅ nM every 10 seconds for 5 minutes using a ThermoMax® Kinetic Microplate Reader.

For K_i determinations, the assay conditions were essentially the same as above except for the following. The concentration of factor Xa was 50 pM, and that of the substrate, in this case a fluorogenic S2765 (i.e., S2765 with AMC tag instead of pNA, California Peptide Research), was over the range of 10 to 500 µM. The test compound and substrate in HBSA buffer were incubated as above, and the reaction was initiated with enzyme-buffer. The data (steady-state

-114-

velocity at various concentrations of the substrate and the inhibitors) of the competitive inhibition was analyzed using the methods described by Segel (Enzyme Kinetics, Wiley Interscience Publications, 1993). A non-linear regression program, Kaleidograph and/or Microsoft Excel, was used to estimate the kinetic parameters (K_m , V_{max} , and K_i) by use of Michaelis-Menten and reciprocal Dixon plot fits.

Determination of Thrombin IC_{50} and K_i Constants

The ability of compounds to act as inhibitors of human thrombin catalytic activity is assessed by determination of that concentration of test substance that inhibits by 50% (IC_{50}) the ability of human thrombin to cleave the chromogenic substrate Chromozym TH (Tosyl-Gly-Pro-Arg-pNA*Ac, Boehringer Mannheim). Typically, 145 μ L human thrombin (0.75 nM, Enzyme Research Laboratories) in a HPB buffer (10 mM HEPES, 100 mM NaCl, 0.05% BSA, 0.1% PEG-8000, pH 7.4) and 5 μ L of test substance in DMSO (2% final) are incubated for 60 minutes at room temperature. Following preheating to 37°C for 5 minutes, to this mixture is added 100 μ L of Chromozym TH (24 μ M final) in HPB buffer. The velocity of Chromozym TH hydrolysis is determined at 37°C by measuring the initial rate of change of the optical density at OD 405 nM every 10 seconds for 5 minutes using a ThermoMax® Kinetic Microplate Reader.

For K_i determinations, the assay conditions were essentially the same as the aforementioned except for the following. The concentration of thrombin used was 50 pM, and that of a fluorogenic Chromozym TH (i.e., Chromozym TH with AMC instead of pNA tag, Novabiochem) was over the range of 1 to 40 μ M. The test compound and substrate in HPB buffer were incubated as above, and the reaction was initiated with enzyme-buffer and run at 24°C. Kinetic analysis was performed as for factor Xa K_i determinations.

Determination of Trypsin IC_{50} and K_i Constants.

The ability of compounds to act as inhibitors of human trypsin catalytic activity is assessed by determination of that concentration of test substance that

-115-

inhibits by 50% (IC₅₀) the ability of human trypsin to cleave the chromogenic substrate S2222 (N-Bz-L-Ile-L-Glu-L-Gly-L-Arg-p-nitroanilide. HCl, DiaPharma). Typically, 145 µL human trypsin (0.5 nM final) in 10 mM HEPES, 150 mM NaCl, 0.1% BSA, and 5 µL of the test substance in DMSO (2% final) are incubated for 60 minutes at room temperature. Following preheating to 37°C for 5 minutes, to this mixture is added 100 µL of S2222 in HBSA buffer (100 µM final), and the velocity of S2222 hydrolysis is determined at 37°C by measuring the optical density at OD 405 nM every 10 seconds over 5 minutes using a ThermoMax® Kinetic Microplate Reader.

For K_i determinations, the assay conditions were essentially the same as the aforementioned except that the reaction was initiated with enzyme-buffer and run at 24°C using a substrate range of 10 to 500 µM. Kinetic analysis was performed as for factor Xa K_i determinations.

Determination of Tissue Factor/Factor VIIa IC₅₀

The ability of compounds to act as inhibitors of the catalytic activity of human tissue factor/factor VIIa complex is assessed by determination of that concentration of test substance that inhibits by 50% (IC₅₀) the ability of a complex of human recombinant tissue factor/factor VIIa to cleave the chromogenic substrate Spectrozyme VIIa (CH₃SO₂-D-CHA-Arg-pNA*AcOH, American Diagnostica). Typically, 50 µL human factor VIIa (Enzyme Research Laboratories) is incubated for 10 minutes as a 1:1 mixture (5 nM final each) with 95 µL recombinant human tissue factor (American Diagnostica) in a modified HBSA buffer (10 mM Hepes, 5 mM CaCl₂, 0.1% BSA, pH 8.0). Then 5 µL of the test substance in DMSO (2% final) is added and incubated for 60 minutes at room temperature. Following preheating to 37°C for 5 minutes, to this mixture is added 100 µL of Spectrozyme VIIa (500 µM final) in modified HBSA, and the velocity of Spectrozyme VIIa hydrolysis is determined at 37°C by measuring the optical density at an OD₄₀₅ nM every 10 seconds over 5 minutes using a ThermoMax® Kinetic Microplate Reader.

-116-

In Vitro Assay for Human Prothrombinase

This assay demonstrates the ability of test compounds of the invention to inhibit the human prothrombinase (PTase) complex (typically comprising of human factor Va, human factor Xa, Ca^{2+} , and phospholipid moiety) and thereby the subsequent cleavage of prothrombin to yield thrombin. For determination of IC_{50} (PTase) of the compounds of the invention, PTase activity was expressed by thrombin activity.

PTase reaction was performed in 100 μL of mixture containing PTase (20 μM) PCPS (Avanti Polar Lipids following a procedure modified from Barenholz et al., *Biochemistry*, 1977;16:2806-2810) in a 30:70 ratio, 2.5 nM human factor Va (Enzyme Research Laboratories) and 2.5 pM human factor Xa (Enzyme Research Laboratories) in modified HEPES buffer (10 mM Hepes, 150 mM NaCl, 0.1% PEG-8000, 0.05% BSA, 2.5 mM CaCl_2 , pH 7.4), 3 μM human prothrombin (Enzyme Research Laboratories) and varied concentrations of the test compounds (1 nM to 100 μM in DMSO, 2% final). Reaction was started by co-incubating PTase with test compound for 60 minutes at room temperature, followed by addition of prothrombin for 6 minutes at room temperature. Next, the reaction was quenched by the addition of 100 μL of 20 mM EDTA. Activity of the thrombin (product) is then measured in the presence of 50 μL S2238 (250 μM final, H-D-Phe-Pip-Arg-pNA*Ac, DiaPharma) as substrate by measuring the change at 37°C in OD₄₀₅ nM for 5 minutes at 10 second intervals using a ThermoMax® Kinetic Microplate Reader.

Example 5 in this assay has an IC_{50} of 0.00017 μM

Determination of Prothrombin Time (PT)

Rat, rabbit, dog, and human blood (typically 1.8 mL) was collected and added to a sodium citrate solution (3.8%) to afford a 1:10 dilution. After centrifugation (2000 g for 10 minutes), the blood plasma was stored at -70°C to 0°C. Conventional prothrombin time (PT) tests were carried out in the presence of various concentrations of test compound and the concentration of test compound required to double the clotting time determined. Typically, the test compound

-117-

(50 μ L volume of varying concentrations 0.1 μ M to 1000 μ M) and blood plasma (100 μ L volume) were incubated at 37°C for 10 minutes, and then tissue thromboplastin, typically Neoplastine from American Bioproducts, with calcium was added. Fibrin formation and the time required for a clot to form were
5 determined using an automated ST4 Clot Detection System in duplicate.

In an ex-vivo modification of this assay, drug was administered intravenously or orally to a group of rats or rabbits. At various times blood samples were collected, and the PT coagulation assay as described above were performed.

10 Arterio-Venous Shunt Stasis Antithrombotic Model

In vivo measurements of antithrombotic activity were performed according to the procedure of Vogel et al., *Thromb. Res.*, 1989;54:399-410. Briefly, the vena cava was exposed, collateral veins were ligated, and sutures were loosely located around the inferior vena cava. These sutures were tightened after drug
15 administration to induce stasis within the ligated portion of the vena cava. After an appropriate time, the thrombus was isolated and weighed. The effect of varying drug concentrations administered intravenously or orally on thrombus mass reflected antithrombotic activity.

Alternatively, and according to the procedure of Smith et al., *Br. J. Pharmacol.*, 1982;77:29-38, the left jugular and right carotid artery were exposed and cannulated. A shunt, which contains silk threads or preweighed cotton, is then inserted which connects the two cannulated vessels. Once drug has been
20 administered, the shunt is closed, and the thrombus that forms on the foreign surface in the shunt is removed after a period of time. Clot weight then reflects
25 antithrombotic activity.

Arterial Thrombosis Model

FeCl₃ Induced Carotid Arterial Injury Model

The FeCl₃ induced injury to the carotid artery in rats was induced according to the method described by Kurz K.D., Main R.W., Sandusky G.E.,

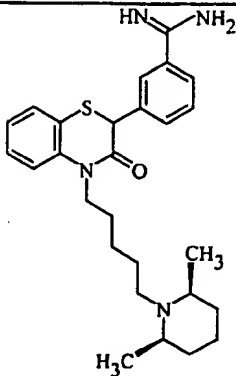
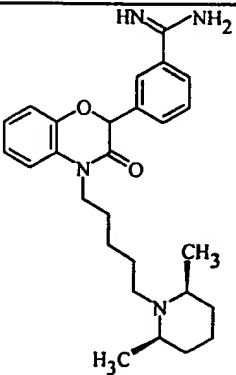
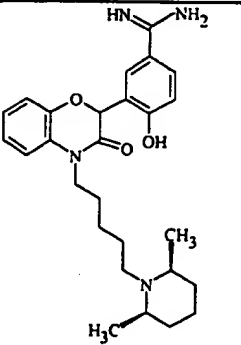
-118-

Thrombosis Research, 1990;60:269-280 and Schumacher W.A. et al.,
J. Pharmacology and Experimental Therapeutics, 1993;267:1237-1242.

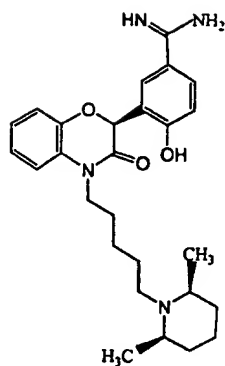
Male, Sprague-Dawley rats (375-410 g) were anesthetized with urethane (1500 mg/kg ip). Animals were laid on a 37°C heating pad. The carotid artery was exposed through a midline cervical incision. Careful blunt dissection was used to isolate the vessel from the carotid sheath. Using forceps, the artery was lifted to provide sufficient clearance to insert two small pieces of polyethylene tubing (PE-205) underneath it. A temperature probe (Physitemp MT23/3) was placed between one of the pieces of tubing and the artery. Injury was induced by topical application on the carotid artery above the temperature probe of a small disc (3 mm dia.) of Whatman No. 1 filter paper previously dipped in a 35% solution of FeCl₃. The incision area was covered with aluminum foil in order to protect the FeCl₃ from degradation by light. The vessel temperature was monitored for 60 minutes after application of FeCl₃ as an indication of blood flow. Vessel temperature changes were recorded on a thermistor (Cole-Palmer Model 08533-41).

The time between the FeCl₃ application and the time at which the vessel temperature decreased abruptly (>2.4°C) was recorded as the time to occlusion of the vessel. The fold shift in mean occlusion time (MOT), therefore, refers to the time to occlusion in drug treated animal divided by control time to occlusion. Inhibitor compounds were given as an IV bolus (0.75 mg/kg) followed immediately by an IV infusion (50 µg/kg/min via femoral vein).

-119-

Structure	Name	Thrombin IC ₅₀ μM	Trypsin IC ₅₀ μM	Xa IC ₅₀ μM	VIIa % inhib. @ 100 μM
	3-(4-5-[(2 <i>R</i> ,6 <i>S</i>)-2,6-Dimethyltetrahydro-1(2 <i>H</i>)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2 <i>H</i> -1,4-benzothiazin-2-yl)-benzenecarboximidamide (Example 3)	1.78	0.782	0.108	31
	3-(4-5-[(2 <i>R</i> ,6 <i>S</i>)-2,6-Dimethyltetrahydro-1(2 <i>H</i>)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2 <i>H</i> -1,4-benzoxazin-2-yl)-benzenecarboximidamide (Example 2)	2.020	0.474	0.007	30
	3-(4-5-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethyltetrahydro-1(2 <i>H</i>)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2 <i>H</i> -1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide (Example 5)	1.03	0.38	<0.001	29

-120-



3-((2S)-4-5- [(2R,6S)-2,6- dimethyltetrahydro- 1(2H)- pyridinyl]pentyl-3- oxo-3,4-dihydro-2H- 1,4-benzoxazin-2- yl)-4- hydroxybenzenecarb oximidamide	1.39	0.75	0.003 (K _i 0.076 nM)	37
(Example 6)				

Biological Data of Examples 2 and 5

In Vitro Diluted Prothrombin Time (dPT) Assay

The effects of Examples 2 and 5 on dPT were evaluated using pooled plasma from rabbits, dogs, and human volunteers. Both compounds concentration-
 5 dependently prolonged dPT and displayed a similar potency in rabbit and dog plasma. In human plasma, however, Example 5 was more potent than Example 2 by approximately one order of magnitude. The concentrations which caused
 5-fold prolongation of dPT for Examples 2 and 5 were 1.1 and 0.97 μ M in rabbit plasma, 1.8 and 1.2 μ M in dog plasma, and 0.53 and 0.063 μ M in human plasma,
 10 respectively.

-121-

In Vitro Diluted Prothrombin Time (dPT) Assay			
	2X	5X	10X
Rabbit			
DX-9065a (μ M)	1.4	21.8	96.8
Example 2 (μ M)	0.33	1.1	2.4
Example 5 (μ M)	0.44	0.97	1.86
Dog			
DX-9065a (μ M)	2.5	51.1	118.6
Example 2 (μ M)	0.57	1.8	4.9
Example 5 (μ M)	0.84	1.2	1.81
Human			
DX-9065a (μ M)	0.06	0.53	1.3
Example 2 (μ M)	0.17	0.53	1.2
Example 5 (μ M)	0.0069	0.063	0.157

The data is the concentrations that cause 2-, 5-, and 10-fold prolongation of baseline values of dPT.

DX-9065a is a reference factor Xa inhibitor

The effects of Example 2 on thrombosis and hemostasis has been studied in a rabbit veno-venous shunt model of thrombosis. In that model, a plastic shunt which contains cotton thread was inserted into abdominal vena cava and thrombus developed inside the shunt under control conditions. The end points of the experiment are the time to occlusion (TTO) and thrombus weight. Example 2 was given to the rabbit *via* jugular vein as a single bolus followed by constant infusion for 140 minutes. Three doses have been tested in a total of 15 rabbits (5 rabbits in each group): 30 μ g/kg + 1 μ g/kg/min, 60 μ g/kg + 2 μ g/kg/min, and 90 μ g/kg + 3 μ g/kg/min. Example 2 dose-dependently prolonged the time to occlusion and reduced the net thrombus weight. In the highest dose group, TTO was increased from 16.8 \pm 5.4 minutes under control condition to 98.2 \pm 21.8 minutes with no occlusive thrombus formation during the 120-minute test period in 4 out of 5 animals. The net thrombus weight was reduced from 56.4 \pm 4.3 to 21.3 \pm 7.8 mg in that group. Example 2, at the highest dose, prolonged aPTT, TT, PT, and bleeding time by 5.4-, 1.5-, 1.8-, and 2.5-fold, respectively. In contrast, there were only slight increases for ACT in all 3 groups.

The foregoing biological tests have been used to establish the compounds of this invention are useful for preventing and treating thrombotic disorders, for example venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial

-122-

embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, first or recurrent myocardial infarction, unstable angina, and cerebral infarction, stroke, atherosclerosis.

5 The compounds of the present invention can be administered alone or in combination with one or more therapeutic agents. These include, for example, other anticoagulant, antiplatelet, or platelet inhibitory agents which include non-steroidal anti-inflammatory agents such as aspirin, ibuprofen, naproxen sodium, indomethacin, piroxicam and ticlopidine, thrombin inhibitors such as argatroban, efegatran, inogatran, factor VIIa inhibitors, thrombolytic or fibrinolytic agents
10 such as tissue plasminogen activator, urokinase or streptokinase, and GP IIb-IIa antagonists.

The compounds are thus well suited to formulation for convenient administration to mammals for the prevention and treatment of such disorders. The following examples further illustrate typical formulations provided by the
15 invention.

Formulation 1

Ingredient	Amount
compound of Formulas 1-8	200 mg
sodium benzoate	5 mg
isotonic saline	1000 mL

The above ingredients are mixed and dissolved in the saline for IV administration to a human suffering from, for example, arterial thrombosis.

-123-

Formulation 2

Ingredient	Amount
compound of Formulas 1-8	100 mg
cellulose, microcrystalline	400 mg
stearic acid	5 mg
silicon dioxide	10 mg
sugar, confectionery	50 mg

The ingredients are blended to uniformity and pressed into a tablet that is well suited for oral administration to a human for preventing, for example, cerebral infarction.

5 Formulation 3

Ingredient	Amount
compound of Formulas 1-8	200 mg
starch, dried	250 mg
magnesium stearate	10 mg

The ingredients are combined and milled to afford material suitable for filling hard gelatin capsules administered to humans suffering from, for example, venous thrombosis.

Formulation 4

Ingredient	Amount % wt./wt.
compound of Formulas 1-8	1
Polyethylene glycol 1000	74.5
Polyethylene glycol 4000	24.5

10 The ingredients are combined via melting and then poured into molds containing 2.5 g total weight.

-124-

Formulation 5

Ingredient	Amount % wt./wt.
compound of Formulas 1-8	0.1%
Propellant 11/12	98.9%
Oleic acid	1%

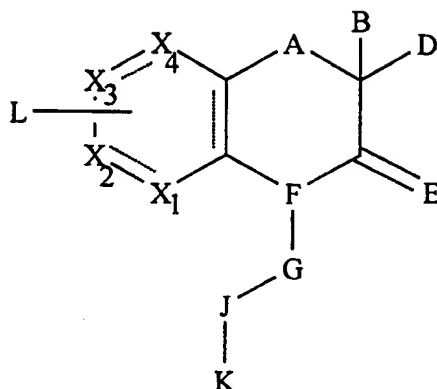
The ingredients are dispersed in oleic acid with the propellant. The mixture is added to an aerosol container fitted with a metering device.

-125-

CLAIMS

What is claimed is:

1. A compound according to Formula 1



1

5 or stereoisomers or pharmaceutically acceptable salt forms or prodrugs thereof, wherein:

A is selected from O, S, S(=O), S(=O)(=O), OCH₂, CH₂O, SCH₂,

S(=O)CH₂, S(=O)(=O)CH₂, CH₂S, CH₂S(=O), CH₂S(=O)(=O);

B is selected from cycloalkyl, heteroalkyl, cycloalkylalkyl,

10 heteroalkylalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, each optionally substituted with R₁ and R₂;

D is selected from H, alkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl,

heteroalkylalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, each optionally substituted with R₁ and R₂;

15 E is absent or selected from O, S, NH;

F is selected from N, NCH₂, CH₂N;

G is absent or selected from alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl, cycloalkyl interrupted by one or more heteroatoms;

20 J is absent or selected from aryl or heterocycle each optionally substituted with R₁ and R₂;

-126-

- K is absent or selected from an alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl interrupted by one or more heteroatoms, cycloalkylalkyl interrupted by one or more heteroatoms, each optionally substituted with R₁ and R₂;
- 5 L is selected from H, chlorine, fluorine, bromine, iodine, OH, O(alkyl), amine, alkyl, fluoroalkyl, amide, NO₂, SH, S(O)_n(alkyl), SO₃H, SO₃alkyl, aldehyde, ketone, acid, ester, urea, Oalkylamide, Oalkylester, Oalkylacid, Nalkylacid, alkylamine, alkylamide, alkylketone, alkylacid, alkylester, alkylurea, Nalkylamide, Nalkylester, NC(=O)alkyl, NC(=O)aryl, NC(=O)cycloalkyl, NC(=O)cycloalkylalkyl, NC(=O) alkylaryl, R₁, R₂, nitrile;
- 10 R₁ is selected from H, amine, alkylamine, amide, C(=NH)NHNH₂, alkylC(=NH)NHNH₂, C(=NH)NHOH, alkylC(=NH)NHOH, NHC(=NH)NH₂, alkylNHC(=NH)NH₂, C(=S)NH₂, alkylC(=S)NH₂, C(=NH)alkyl, alkylC(=NH)alkyl, C(=NR₃)N(R₄)(R₅), alkylC(=NR₃)N(R₄)(R₅);
- 15 R₂ is selected from H, chlorine, fluorine, bromine, iodine, OH, Oalkyl, amine, alkylaldehyde, alkylamide, alkylester, alkylketone, alkylacid, Oalkylamide, Oalkylacid, Oalkylester, aminealkylacid, aminealkylamide, aminealkylester, NC(=O)alkyl, NC(=O)aryl, NC(=O)cycloalkyl, NC(=O)alkylaryl, alkylamine, amide, aldehyde, ester, ketone, NO₂, SH, S(O)_n(C₁₋₁₀alkyl), SO₃H, SO₃alkyl, CHO, acid, alkyl, C(=NH)alkyl, C(=NH)NHNH₂, alkylC(=NH)NHNH₂, C(=NH)NHOH, alkylC(=NH)NHOH, NHC(=NH)NH₂, alkylNHC(=NH)NH₂, C(=S)NH₂, alkylC(=S)NH₂, alkylC(=NH)alkyl, C(=NR₃)N(R₄)(R₅), alkylC(=NR₃)N(R₄)(R₅);
- 20 R₃, R₄, and R₅ are a hydrogen atom, alkyl group having 1 to 4 carbon atoms optionally interrupted by a heteroatom, or R₄ and R₅ are bonded to form -(CH₂)_p-W-(CH₂)_q-, wherein p and q are an
- 25
- 30

-127-

integer of 2 or 3, a certain position on the methylene chain is unsubstituted or substituted by an alkyl group having 1 to 4 carbon atoms, W is a direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{R}_6)-$, or $-\text{S}(\text{O})_r-$ wherein R_6 is H or alkyl, and r is 0 or 1 or 2;

5 n is selected from 0, 1, 2;

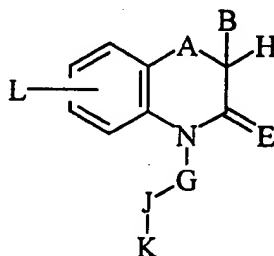
X_1 is C or N;

X_2 is C or N;

X_3 is C or N; and

X_4 is C or N.

10 2. A compound according to Claim 1 wherein the compound is according to Formula 2

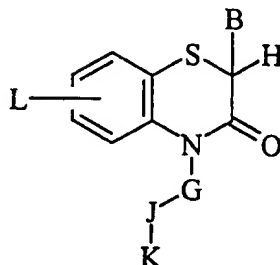


2

or stereoisomers or pharmaceutically acceptable salts, esters, amides or prodrugs thereof, wherein A, B, E, G, J, K, and L are defined as above.

-128-

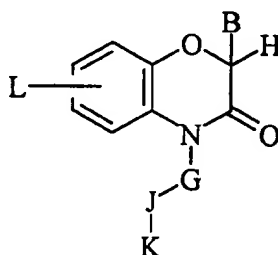
3. A compound according to Claim 1 wherein the compound is according to Formula 3



3

- 5 or stereoisomers or pharmaceutically acceptable salts, esters, amides or prodrugs thereof, wherein B, G, J, K, and L are defined as above.

4. A compound according to Claim 1 wherein the compound is according to Formula 4

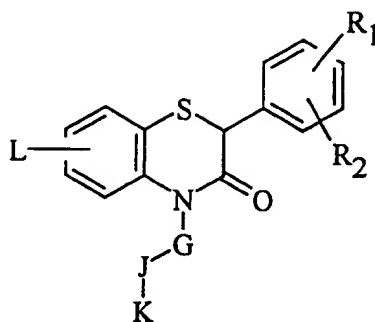


4

- 10 or stereoisomers or pharmaceutically acceptable salts, esters, amides or prodrugs thereof, wherein B, G, J, K, and L are defined as above.

-129-

5. A compound according to Claim 1 wherein the compound is according to Formula 5

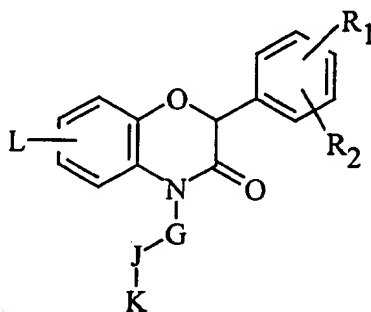


5

or stereoisomers or pharmaceutically acceptable salts, esters, amides or
prodrugs thereof, wherein R₁, R₂, G, J, K, and L are as defined above.

5

6. A compound according to Claim 1 wherein the compound is according to Formula 6



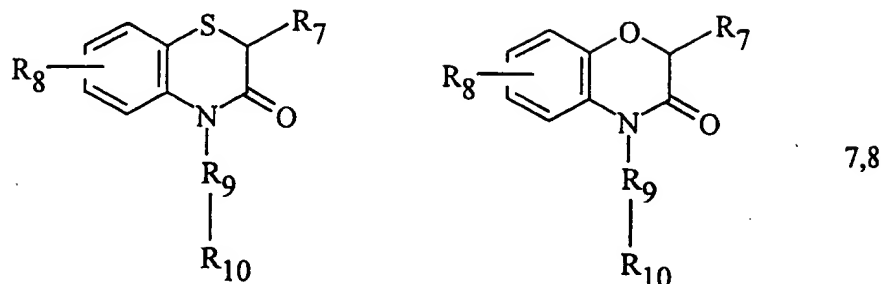
6

or stereoisomers or pharmaceutically acceptable salts, esters, amides or
prodrugs thereof, wherein R₁, R₂, G, J, K, and L are as defined above.

10

-130-

7. A compound according to Formulas 7 and 8



or stereoisomers or pharmaceutically acceptable salt forms or prodrugs thereof,

5 wherein

R₇ is (3-amidino)phenyl, (3-hydroxy)phenyl,
 [3-hydroxylamino(imino)methyl]-phenyl,
 [3-hydrazino(imino)methyl]-phenyl, (3-aminomethyl)phenyl,
 (3-amino)phenyl, (3-methylamino)phenyl,
 10 (3-dimethylamino)phenyl, (5-amidino-2-hydroxy)phenyl,
 (5-amidino-2-methoxy)phenyl, (1-amidino)piperid-3-yl,
 (1-amidino)pyrrolid-3-yl, (5-amidino)thien-2-yl, (5-amidino)furan-
 2-yl, (5-amidino)-1,3-oxazol-2-yl, (2-amidino)-1,3-oxazol-5-yl,
 1H-pyrazol-5-yl, tetrahydro-1H-pyrazol-3-yl,
 15 (1-amidino)tetrahydro-1H-pyrazol-3-yl, (2-amidino)-1H-imidazol-
 4-yl, (2-amino)-1H-imidazol-4-yl, (5-amidino)-1H-imidazol-2-yl,
 (5-amino)-1H-imidazol-2-yl, pyridin-3-yl, (4-amino)pyridin-3-yl,
 (4-dimethylamino)pyridin-3-yl, (6-amino)pyridin-2-yl,
 (6-amidino)pyridin-2-yl, (2-amino)pyridin-4-yl,
 20 (2-amidino)pyridin-4-yl, (2-amidino)pyrimid-4-yl,
 (2-amino)pyrimidin-4-yl, (4-amidino)pyrimid-2-yl,
 (4-amino)pyrimidin-2-yl, (6-amidino)pyrazin-2-yl,
 (6-amino)pyrazin-2-yl, (4-amidino)-1,3,5-triazin-2-yl, (4-amino)-
 1,3,5-triazin-2-yl, (3-amidino)-1,2,4-triazin-5-yl, (3-amino)-1,2,4-
 25 triazin-5-yl, (3-amidino)benzyl, (3-amino)benzyl,
 (3-aminomethyl)benzyl, (1-amidino)piperid-3-ylmethyl,
 (1-amidino)pyrrolid-3-ylmethyl, (5-amidino)thien-2-ylmethyl,

-131-

- (5-amidino)furan-2-ylmethyl, (5-amidino)oxazol-2-ylmethyl,
 (2-amidino)imidazol-5-ylmethyl, (5-amidino)imidazol-2-ylmethyl,
 (6-amidino)pyridin-2-ylmethyl, (6-amino)pyridin-2-ylmethyl,
 (2-amidino)pyrimidin-4-ylmethyl, (2-amino)pyrimidin-4-ylmethyl,
 5 (4-amidino)pyrimidin-2-ylmethyl, (4-amino)pyrimidin-2-ylmethyl,
 (6-amidino)pyrazin-2-ylmethyl, (6-amino)pyrazin-2-ylmethyl,
 3-aminocyclohexyl, 3-amidinocyclohexyl,
 3-aminocyclohexylmethyl, 3-amidinocyclohexylmethyl,
 3-aminocyclopentyl, 3-amidinocyclopentyl, and
 10 3-aminocyclopentylmethyl, and 3-amidinocyclopentylmethyl;
 R₈ is Br, I, C₂H₅, H, Cl, F, SH, SMe, CF₃, CH₃, CO₂H, CO₂Me, CN,
 C(=NH)NH₂, C(=NH)NHOH, C(=NH)NHNH₂, C(=O)NH₂,
 CH₂OH, CH₂NH₂, NO₂, OH, OMe, OCH₂Ph, OCH₂CO₂H,
 O(CH₂)₂CO₂H, O(CH₂)₃CO₂H, NHCH₂CO₂H,
 15 NH(CH₂)₂CO₂H, NH(CH₂)₃CO₂H, OCH₂CH₂OH, OCH₂(1H-
 tetrazol-5-yl), NH₂, NHButyl, NMe₂, NHPH, NHCH₂Ph,
 NHC(=O)Me, NHC(=O)c-Hexyl, NHC(=O)CH₂c-Hexyl,
 NHC(=O)Ph, NHC(=O)CH₂Ph, NHS(=O)₂Me, NHS(=O)₂c-
 Hexyl, NHS(=O)₂CH₂c-Hexyl, NHS(=O)₂Ph, and
 20 NHS(=O)₂CH₂Ph;
 R₉ is (CH₂)₅, (CH₂)₄, (CH₂)₆, CH₂C(=O)NHCH₂CH₂,
 CH₂CH₂NHC(=O)CH₂, (CH₂)₂NH(CH₂)₂, (CH₂)₂O(CH₂)₂,
 C₆H₄, CH₂C₆H₄, C₆H₄CH₂, C₆H₁₀, CH₂C₆H₁₀, C₆H₁₀CH₂,
 C₅H₈, CH₂C₅H₈, C₅H₈CH₂, and CH₂CH=CHCH₂CH₂; and
 25 R₁₀ is 2,6-dimethylpiperidinyl, 2,2,6,6-tetramethyl-piperidinyl-4-one,
 piperidinyl, 2,2,6,6-tetramethylpiperidinyl, (2-carboxy)piperidinyl,
 (3-carboxy)piperidinyl, (4-carboxy)piperidinyl,
 3,5-dimethylpiperidinyl, (4-hydroxy)piperidinyl,
 (2-imino)piperidinyl, piperidin-4-one-yl,
 30 (2-dimethylaminomethyl)-piperidinyl, (4-dimethylamino)-

-132-

piperidinyl, (4-sulphonyloxy)-piperidinyl, (2-phenyl)piperidinyl,
 2,5-dimethylpyrrolidinyl, pyrrolidinyl, (2-carboxy)pyrrolidinyl,
 (3-N-acetyl-N-methyl)pyrrolidinyl, (3-amino)pyrrolidinyl,
 (2,5-bis-methoxymethyl)-pyrrolidinyl, 2-hydroxymethyl-
 5 pyrrolidinyl, 2-hydroxymethyl-5-methyl-pyrrolidinyl,
 diisopropylamino, diethylamino, methylamino, 1-methyl-4,5-
 dihydro-1H-imidazol-2-yl, 2,5-dimethyl-1H-1-imidazolyl,
 morpholinyl, 2,6-dimethylmorpholinyl, piperazinyl,
 2,6-dimethylpiperazinyl, 1H-pyrazolyl, tetrahydro-1H-pyrazolyl,
 10 and 2,5-dimethyltetrahydro-1H-1-pyrazolyl.

8. A compound according to Claim 7 wherein R₇ is (2-hydroxy, 5-amidino)phenyl.
9. A compound according to Claim 7 wherein R₈ is H.
10. A compound according to Claim 7 wherein R₉ is (CH₂)₅.
- 15 11. a compound according to Claim 7 wherein R₁₀ is 2,6-dimethylpiperidinyl.
12. A compound according to Claim 7 wherein R₈ is H, R₉ is (CH₂)₅, and R₁₀ is 2,6-dimethylpiperidinyl.
13. A compound according to Claim 7 wherein R₈ is H, R₉ is (CH₂)₅, and R₁₀ is 2,5-dimethylpyrrolidinyl.
- 20 14. A compound which is:
 3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-
 3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-4-
 methoxybenzenecarboximidamide;
 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-
 25 3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

-133-

- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(3-hydroxyphenyl)-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-*N*-hydroxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-*N*-hydroxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidohydrazide;
- 2-[3-(Aminomethyl)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-(3-Aminophenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-[3-(methylamino)phenyl]-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-[3-(Dimethylamino)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-4-hydroxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)tetrahydro-1(2*H*)-pyridinecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-pyrrolidinecarboximidamide;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-thiophenecarboximidamide;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-furancarboximidamide;

-134-

- 2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,3-oxazole-5-carboximidamide;
- 5 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,3-oxazole-2-carboximidamide;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(1*H*-pyrazol-5-yl)-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 10 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1-pyrazolidinecarboximidamide;
- 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1*H*-imidazole-2-carboximidamide;
- 15 2-(2-Amino-1*H*-imidazol-4-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1*H*-imidazole-5-carboximidamide;
- 20 2-(5-Amino-1*H*-imidazol-2-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(3-pyridinyl)-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 25 2-(4-Amino-3-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-[4-(Dimethylamino)-3-pyridinyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-(6-Amino-2-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 30 6-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyridinecarboximidamide;

-135-

- 2-(2-Amino-4-pyridinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyridinecarboximidamide;
- 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyrimidinecarboximidamide;
- 2-(2-Amino-4-pyrimidinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-4-pyrimidinecarboximidamide;
- 2-(4-Amino-2-pyrimidinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 6-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-2-pyrazinecarboximidamide;
- 2-(6-Amino-2-pyrazinyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 4-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,3,5-triazine-2-carboximidamide;
- 2-(4-Amino-1,3,5-triazin-2-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 5-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-1,2,4-triazine-3-carboximidamide;
- 2-(3-Amino-1,2,4-triazin-5-yl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]benzenecarboximidamide;

-136-

- 2-(3-Aminobenzyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-[3-(Aminomethyl)benzyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 5 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]tetrahydro-1(2*H*)-pyridinecarboximidamide;
- 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1-pyrrolidinecarboximidamide;
- 10 5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-thiophenecarboximidamide;
- 5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-furancarboximidamide;
- 15 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1,3-oxazole-5-carboximidamide;
- 20 5-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1*H*-imidazole-2-carboximidamide;
- 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-1*H*-imidazole-5-carboximidamide;
- 25 6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyridinecarboximidamide;
- 2-[(6-Amino-2-pyridinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 30 4-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyrimidinecarboximidamide;

-137-

- 2-[(2-Amino-4-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-4-pyrimidinecarboximidamide;
- 2-[(4-Amino-2-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyrazinecarboximidamide;
- 2-[(6-Amino-2-pyrazinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 2-(3-Aminocyclohexyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)cyclohexanecarboximidamide;
- 2-[(3-Aminocyclohexyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]cyclohexanecarboximidamide;
- 2-(3-Aminocyclopentyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)cyclopentanecarboximidamide;
- 2-[(3-Aminocyclopentyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;
- 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]cyclopentanecarboximidamide;

-138-

- 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-(4-6-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]hexyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 5 2-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)-*N*-2-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]ethylacetamide;
- 3-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)-*N*-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]methylpropanamide;
- 10 3-4-[2-(2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethylamino)ethyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-[4-(2-2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethoxyethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 15 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]phenyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 20 3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylphenyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 25 3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 30 3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylcyclohexyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

-139-

- 3-(4-3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclopentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 5 3-[4-(3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclopentylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 3-[4-(3-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylcyclopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 10 3-(4-(*E*)-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]-2-pentenyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-[3-Oxo-4-(5-piperidinopentyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 15 3-3-Oxo-4-[5-(2,2,6,6-tetramethylpiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-2-piperidinecarboxylic acid;
- 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-3-piperidinecarboxylic acid;
- 20 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-4-piperidinecarboxylic acid;
- 3-4-[5-(3,5-Dimethylpiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 25 3-4-[5-(4-Hydroxypiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(2-Iminopiperidino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 30 3-3-Oxo-4-[5-(4-oxopiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-[4-(5-2-[(Dimethylamino)methyl]piperidinopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;

-140-

- 3-(4-5-[4-(Dimethylamino)piperidino]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-4-piperidinesulfonic acid;
- 5 3-3-Oxo-4-[5-(2-phenylpiperidino)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(2,5-Dimethyl-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 10 3-3-Oxo-4-[5-(1-pyrrolidinyl)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]-2-pyrrolidinecarboxylic acid;
- N*-1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)pentyl]tetrahydro-1*H*-pyrrol-3-yl-*N*-methylacetamide;
- 15 3-4-[5-(3-Amino-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-(4-5-[2,5-Bis(methoxymethyl)-1-pyrrolidinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 20 3-(4-5-[2-(Hydroxymethyl)-1-pyrrolidinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-(4-5-[2-(Hydroxymethyl)-5-methyl-1-pyrrolidinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-4-[5-(Diisopropylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 25 3-4-[5-(Diethylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(Methylamino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 30 3-4-[5-(1-Methyl-1*H*-imidazol-2-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(2,5-Dimethyl-1*H*-imidazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;

-141-

- 3-[4-(5-Morpholinopentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 3-4-[5-(3,5-Dimethylmorpholino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 5 3-[3-Oxo-4-(5-piperazinopentyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 3-4-[5-(2,6-Dimethylpiperazino)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 10 3-3-Oxo-4-[5-(1*H*-pyrazol-1-yl)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-[3-Oxo-4-(5-tetrahydro-1*H*-pyrazol-1-yl)pentyl]-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 3-4-[5-(2,5-Dimethyltetrahydro-1*H*-pyrazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 15 3-(6-Chloro-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-fluoro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 20 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-sulfanyl-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(methylsulfanyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 25 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 30 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

-142-

- 2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid;
- 5 Methyl 2-3-[amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate;
- 3-(6-Cyano-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 10 2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboximidamide;
- 2-3-[amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-*N*-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboximidamide;
- 15 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-[hydrazino(imino)methyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide;
- 20 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(hydroxymethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 25 3-(6-(Aminomethyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 30 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

-143-

- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-methoxy-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 5 3-(6-(Benzyloxy)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)oxy]acetic acid;
- 10 3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)oxy]propanoic acid;
- 4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)oxy]butanoic acid;
- 15 2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)amino]acetic acid;
- 3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)amino]propanoic acid;
- 20 4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)amino]butanoic acid;
- 25 3-[4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-(2-hydroxyethoxy)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-(2*H*-1,2,3,4-tetraazol-5-ylmethoxy)-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl]benzenecarboximidamide;
- 30 3-(6-Amino-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

-144-

- 3-(6-(Butylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 5 3-(6-(Dimethylamino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 10 3-(6-(Anilino)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 15 *N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)acetamide;
- N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)cyclohexanecarboxamide;
- 20 *N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)-2-cyclohexylacetamide;
- N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)benzenecarboxamide;
- 25 *N*-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)-2-phenylacetamide;
- 30 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-6-[(methylsulfonyl)amino]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide;
- 3-6-[(Cyclohexylsulfonyl)amino]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

-145-

- 3-(6-[(Cyclohexylmethyl)sulfonyl]amino-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
- 3-4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-6-[(phenylsulfonyl)amino]-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylbenzenecarboximidamide; or
- 3-(6-[(Benzylsulfonyl)amino]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;
15. A compound which is:
- 3-(4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-4-methoxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-(3-hydroxyphenyl)-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-hydroxybenzenecarboximidamide;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidohydrazide;
- 2-[3-(Aminomethyl)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 2-(3-Aminophenyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-[3-(methylamino)phenyl]-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 2-[3-(Dimethylamino)phenyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;

-146-

- 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide;
- 5 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)tetrahydro-1(2H)-pyridinecarboximidamide;
- 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1-pyrrolidinecarboximidamide;
- 10 5-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-2-thiophenecarboximidamide;
- 5-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-2-furancarboximidamide;
- 15 2-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1,3-oxazole-5-carboximidamide;
- 5-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1,3-oxazole-2-
- 20 carboximidamide;
- 4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2-(1H-pyrazol-5-yl)-2H-1,4-benzoxazin-3(4H)-one;
- 4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2-tetrahydro-1H-pyrazol-3-yl-2H-1,4-benzoxazin-3(4H)-one;
- 25 5-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1-pyrazolidinecarboximidamide;
- 4-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1H-imidazole-2-
- 30 carboximidamide;
- 2-(2-Amino-1H-imidazol-4-yl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;

-147-

- 2-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1H-imidazole-5-carboximidamide;
- 5 2-(5-Amino-1H-imidazol-2-yl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2-(3-pyridinyl)-2H-1,4-benzoxazin-3(4H)-one;
- 2-(4-Amino-3-pyridinyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 10 2-[4-(Dimethylamino)-3-pyridinyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 2-(6-Amino-2-pyridinyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 15 6-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-2-pyridinecarboximidamide;
- 2-(2-Amino-4-pyridinyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 4-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-2-pyridinecarboximidamide;
- 20 4-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-2-pyrimidinecarboximidamide;
- 2-(2-Amino-4-pyrimidinyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 25 2-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-4-pyrimidinecarboximidamide;
- 2-(4-Amino-2-pyrimidinyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 30 6-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-2-pyrazinecarboximidamide;
- 2-(6-Amino-2-pyrazinyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;

-148-

- 4-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1,3,5-triazine-2-carboximidamide;
- 5 2-(4-Amino-1,3,5-triazin-2-yl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 5-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1,2,4-triazine-3-carboximidamide;
- 10 2-(3-Amino-1,2,4-triazin-5-yl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 3-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]benzenecarboximidamide;
- 15 2-(3-Aminobenzyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 2-[3-(Aminomethyl)benzyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 3-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]tetrahydro-1(2H)-pyridinecarboximidamide;
- 20 3-[(4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-1-pyrrolidinecarboximidamide;
- 5-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-2-thiophenecarboximidamide;
- 25 5-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-2-furancarboximidamide;
- 30 2-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-1,3-oxazole-5-carboximidamide;

-149-

- 5-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-1H-imidazole-2-carboximidamide;
- 5 2-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-1H-imidazole-5-carboximidamide;
- 6-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-2-pyridinecarboximidamide;
- 10 2-[(6-Amino-2-pyridinyl)methyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 4-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-2-pyrimidinecarboximidamide;
- 15 2-[(2-Amino-4-pyrimidinyl)methyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 2-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-4-pyrimidinecarboximidamide;
- 20 2-[(4-Amino-2-pyrimidinyl)methyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 6-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-2-pyrazinecarboximidamide;
- 25 2-[(6-Amino-2-pyrazinyl)methyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 2-(3-Aminocyclohexyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 30 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)cyclohexanecarboximidamide;
- 2-[(3-Aminocyclohexyl)methyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;

-150-

- 3-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]cyclohexanecarboximidamide;
- 5 2-(3-Aminocyclopentyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)cyclopentanecarboximidamide;
- 10 2-[(3-Aminocyclopentyl)methyl]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-2H-1,4-benzoxazin-3(4H)-one;
- 3-[(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]cyclopentanecarboximidamide;
- 15 3-(4-4-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]butyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-(4-6-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]hexyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 20 2-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-N-2-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]ethylacetamide;
- 3-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-N-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]methylpropanamide;
- 25 3-4-[2-(2-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]ethylamino)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-4-(2-2-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]ethoxyethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 30 3-(4-4-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]phenyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-(4-4-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]benzyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;

-151-

- 3-[4-(4-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]methylphenyl)-
3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-
yl]benzenecarboximidamide;
- 5 3-(4-(4-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]cyclohexyl)-3-
oxo-3,4-dihydro-2H-1,4-benzoxazin-2-
yl)benzenecarboximidamide;
- 10 3-[4-(4-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-
pyridinyl]cyclohexylmethyl)-3-oxo-3,4-dihydro-2H-1,4-
benzoxazin-2-yl]benzenecarboximidamide;
- 15 3-[4-(4-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]cyclopentyl)-3-
oxo-3,4-dihydro-2H-1,4-benzoxazin-2-
yl]benzenecarboximidamide;
- 20 3-[4-(3-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-
pyridinyl]cyclopentylmethyl)-3-oxo-3,4-dihydro-2H-1,4-
benzoxazin-2-yl]benzenecarboximidamide;
- 25 3-[4-(3-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-
pyridinyl]methylcyclopentyl)-3-oxo-3,4-dihydro-2H-1,4-
benzoxazin-2-yl]benzenecarboximidamide;
- 30 3-(4-(E)-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]-2-pentenyl)-
3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-
yl]benzenecarboximidamide;
- 25 3-[3-Oxo-4-(5-piperidinopentyl)-3,4-dihydro-2H-1,4-benzoxazin-2-
yl]benzenecarboximidamide;
- 30 3-3-Oxo-4-[5-(2,2,6,6-tetramethylpiperidino)pentyl]-3,4-dihydro-2H-1,4-
benzoxazin-2-yl]benzenecarboximidamide;
- 1-[5-(2-3-[Amino(imino)methyl]phenyl)-3-oxo-2,3-dihydro-4H-1,4-
benzoxazin-4-yl]pentyl]-2-piperidinecarboxylic acid;
- 1-[5-(2-3-[Amino(imino)methyl]phenyl)-3-oxo-2,3-dihydro-4H-1,4-
benzoxazin-4-yl]pentyl]-3-piperidinecarboxylic acid;

-152-

- 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)pentyl]-4-piperidinecarboxylic acid;
- 3-4-[5-(3,5-Dimethylpiperidino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 5 3-4-[5-(4-Hydroxypiperidino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(2-Iminopiperidino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-3-Oxo-4-[5-(4-oxopiperidino)pentyl]-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 10 3-[4-(5-2-[(Dimethylamino)methyl]piperidinopentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 3-(4-5-[4-(Dimethylamino)piperidino]pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 15 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)pentyl]-4-piperidinesulfonic acid;
- 3-3-Oxo-4-[5-(2-phenylpiperidino)pentyl]-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(2,5-Dimethyl-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 20 3-3-Oxo-4-[5-(1-pyrrolidinyl)pentyl]-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)pentyl]-2-pyrrolidinecarboxylic acid;
- 25 N-1-[5-(2-3-[Amino(imino)methyl]phenyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)pentyl]tetrahydro-1H-pyrrol-3-yl-N-methylacetamide;
- 3-4-[5-(3-Amino-1-pyrrolidinyl)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 30 3-(4-5-[2,5-Bis(methoxymethyl)-1-pyrrolidinyl]pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-(4-5-[2-(Hydroxymethyl)-1-pyrrolidinyl]pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;

-153-

- 3-(4-5-[2-(Hydroxymethyl)-5-methyl-1-pyrrolidinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-4-[5-(Diisopropylamino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 5 3-4-[5-(Diethylamino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(Methylamino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 10 3-4-[5-(1-Methyl-1H-imidazol-2-yl)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(2,5-Dimethyl-1H-imidazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-[4-(5-Morpholinopentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 15 3-4-[5-(3,5-Dimethylmorpholino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-[3-Oxo-4-(5-piperazinopentyl)-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 20 3-4-[5-(2,6-Dimethylpiperazino)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-3-Oxo-4-[5-(1H-pyrazol-1-yl)pentyl]-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 25 3-[3-Oxo-4-(5-tetrahydro-1H-pyrazol-1-yl)pentyl]-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-4-[5-(2,5-Dimethyltetrahydro-1H-pyrazol-1-yl)pentyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 3-(6-Chloro-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 30 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-fluoro-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;

-154-

- 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-6-sulfanyl-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 5 3-[4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-(methylsulfanyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 3-[4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 10 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid;
- 15 Methyl 2-3-[amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate;
- 3-(6-Cyano-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 20 2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboximidamide;
- 25 2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-N-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboximidamide;
- 3-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-[hydrazino(imino)methyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 30 2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide;

-155-

- 3-[4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-(hydroxymethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 5 3-(6-(Aminomethyl)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-nitro-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 10 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-(4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-methoxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 15 3-(6-(Benzyloxy)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 20 2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)oxy]acetic acid
- 3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)oxy]propanoic acid;
- 25 4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)oxy]butanoic acid;
- 2-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)amino]acetic acid;
- 30 3-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)amino]propanoic acid;

-156-

- 4-[(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)amino]butanoic acid;
- 5 3-[4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-(2-hydroxyethoxy)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 3-[4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-6-(2H-1,2,3,4-tetraazol-5-ylmethoxy)-3,4-dihydro-2H-1,4-benzoxazin-2-yl]benzenecarboximidamide;
- 10 3-(6-Amino-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-(6-(Butylamino)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 15 3-(6-(Dimethylamino)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-(6-Anilino-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 20 3-(6-(Benzylamino)-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 25 N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)acetamide;
- N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)cyclohexanecarboxamide;
- 30 N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-2-cyclohexylacetamide;

-157-

- N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)benzenecarboxamide;
- 5 N-(2-3-[Amino(imino)methyl]phenyl-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-2-phenylacetamide;
- 3-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-6-[(methylsulfonyl)amino]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide;
- 10 3-(6-[(Cyclohexylsulfonyl)amino]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 3-(6-[(Cyclohexylmethyl)sulfonyl]amino-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide;
- 15 3-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-6-[(phenylsulfonyl)amino]-3,4-dihydro-2H-1,4-benzoxazin-2-ylbenzenecarboximidamide; or
- 3-(6-[(Benzylsulfonyl)amino]-4-5-[(2R,6S)-2,6-dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide.
- 20
16. A compound which is:
- 3-((2R)-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-4-methoxybenzenecarboximidamide;
- 25 3-((2S)-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-4-methoxybenzenecarboximidamide;
- 3-((2R)-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide;
- 30

-158-

- 3-((2S)-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide;
- 5 3-((2R)-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide; or
- 3-((2S)-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)benzenecarboximidamide.
- 10 17. A compound which is:
- 3-((2S)-4-5-[(2R,6S)-2,6-Dimethyltetrahydro-1(2H)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-4-hydroxybenzenecarboximidamide.
- 15 18. A compound of which is:
- 2H-1,4-Benzoxazin-3(4H)-one, 4-[3-(2,6-dimethyl-1-piperidinyl)propyl]-2-phenyl-;
- 4-[5-(2,5-Dimethyl-pyrrolidin-1-yl)-pentyl]-2-phenyl-4H-benzo[1,4]oxazin-3-one;
- 20 2H-1,4-Benzoxazin-3(4H)-one, 4-[5-[bis(1-methylethyl)amino]pentyl]-2-phenyl-;
- 2H-1,4-Benzoxazin-3(4H)-one, 4-[3-(2,5-dimethyl-1-pyrrolidinyl)propyl]-2-phenyl-;
- 2H-1,4-Benzoxazin-3(4H)-one, 4-[3-[bis(1-methylethyl)amino]propyl]-2-phenyl-;
- 25 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-phenyl-4H-benzo[1,4]oxazin-3-one;
- 4-(5-Diethylamino-pentyl)-2-phenyl-4H-benzo[1,4]oxazin-3-one;
- 2-Phenyl-4-(5-pyrrolidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 2-[5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentyl]-
- 30 isoindole-1,3-dione;
- 4-(5-Imidazol-1-yl-pentyl)-2-phenyl-4H-benzo[1,4]oxazin-3-one;

-159-

- 2-(4-Chloro-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-
4H-benzo[1,4]oxazin-3-one;
- 2-(2-Chloro-phenyl)-4-[5-(2,5-dimethyl-pyrrolidin-1-yl)-pentyl]-
4H-benzo[1,4]oxazin-3-one;
- 5 2-(2-Chloro-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-
4H-benzo[1,4]oxazin-3-one;
- 5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-
pentanamidine;
- 2-Phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 10 2-(4-Chloro-phenyl)-4-[5-(2,5-dimethyl-pyrrolidin-1-yl)-pentyl]-
4H-benzo[1,4]oxazin-3-one;
- 2-Phenyl-4-(5-pyrrolidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
compound with trifluoro-acetic acid;
- 3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-
benzonitrile;
- 15 4-[6-(2,5-Dimethyl-pyrrolidin-1-yl)-hexyl]-2-phenyl-4H-
benzo[1,4]oxazin-3-one;
- 3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-
benzamidine;
- 20 2-Naphthalen-2-yl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;
- 4-(5-Amino-pentyl)-2-phenyl-4H-benzo[1,4]oxazin-3-one;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-phenyl-4H-
benzo[1,4]oxazin-3-one;
- 25 6-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;
- 7-Methoxy-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;
- 8-Chloro-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;
- 30 3-Oxo-2-phenyl-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-
benzo[1,4]oxazine-6-carbonitrile;

-160-

4-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-
benzamidine;

1-[5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentyl]-
piperidine-2,6-dione;

5 3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-
propionitrile;

4-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-
butyronitrile;

10 5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-
pentanenitrile;

N-[3-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-
propyl]-guanidine;

N-[5-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-pentyl]-
guanidine;

15 4-(3-Oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-
benzamidine;

2-(4-Methoxy-phenyl)-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

20 7-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

5-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

6-Methoxy-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

25 N-Hydroxy-4-(3-oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-
ylmethyl)-benzamidine;

6-Chloro-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

30 2-(4-Methoxy-phenyl)-4-(5-piperazin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

2-(4-Hydroxy-phenyl)-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

-161-

4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-hydroxy-phenyl)-
4H-benzo[1,4]oxazin-3-one;

2-(4-Methoxy-phenyl)-4-[5-(4-methyl-piperazin-1-yl)-pentyl]-4H-
benzo[1,4]oxazin-3-one;

5 4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-
2H-benzo[1,4]oxazin-2-yl}-benzonitrile;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-
2H-benzo[1,4]oxazin-2-yl}-benzamidine;

10 4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-
2H-benzo[1,4]oxazin-2-yl}-thiobenzamide;

[2-(4-Methoxy-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-
acetic acid;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-
2H-benzo[1,4]oxazin-2-yl}-N-hydroxy-benzamidine;

15 Benzenecarboximidic acid, 4-[3,4-dihydro-4-[5-(2,6-dimethyl-1-
piperidiny]pentyl]-3-oxo-2H-1,4-benzoxazin-2-yl]-, hydrazide;

6-Amino-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-
benzo[1,4]oxazin-3-one;

20 4-(5-Bromo-pentyl)-2-(3,4-dimethoxy-phenyl)-4H-
benzo[1,4]oxazin-3-one;

4-(5-Bromo-pentyl)-2-(3,4,5-trimethoxy-phenyl)-4H-
benzo[1,4]oxazin-3-one;

4-(5-Bromo-pentyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-
3-one;

25 N-[2-(2,6-Dimethyl-piperidin-1-yl)-ethyl]-2-[2-(4-methoxy-
phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetamide;

4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(3,4,5-trimethoxy-
phenyl)-4H-benzo[1,4]oxazin-3-one;

30 2-(3,4-Dimethoxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-
pentyl]-4H-benzo[1,4]oxazin-3-one;

2-(4-Bromo-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-
4H-benzo[1,4]oxazin-3-one;

-162-

- 8-Methyl-2-phenyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
- 2-(4-Benzylamino-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 5 2-(4-Methoxy-phenyl)-4-[5-(2,2,6,6-tetramethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 4-(2-Bromo-ethyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 4-(5-Bromo-pentyl)-2-(3,4-dichloro-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 10 4-(2-Hydroxy-ethyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 2-(3,4-Dichloro-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 15 4-[3-(2,6-Dimethyl-piperidin-1-ylmethyl)-benzyl]-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 4-(2-Amino-ethyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 2-(2,6-Dimethyl-piperidin-1-yl)-N-{2-[2-(4-methoxy-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide;
- 20 4-[5-(2,6-Dimethyl-piperidin-1-yl)-5-oxo-pentyl]-2-(4-methoxy-phenyl)-4H-benzo[1,4]oxazin-3-one;
- 3-{4-[4-(2,6-Dimethyl-piperidin-1-yl)-butyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 25 3-{4-[6-(2,6-Dimethyl-piperidin-1-yl)-hexyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 2-(5-Aminomethyl-2-hydroxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 2-(3-Aminomethyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 30 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-7-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

-163-

- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-methoxy-benzamidine;
- 2-(5-Aminomethyl-2-methoxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]oxazin-3-one;
- 5 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-N-hydroxy-4-methoxy-benzamidine;
- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-N-hydroxy-benzamidine;
- 10 3-{7-Chloro-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 4-(5-Bromo-pentyl)-2-phenyl-4H-benzo[1,4]oxazin-3-one;
- 3-[3-Oxo-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;
- 15 N-{2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl}-acetamide;
- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-hydroxy-benzamidine;
- 3-[4-(5-Diisopropylamino-pentyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzamidine;
- 20 3-(4-{4-[(Diisopropylamino)-methyl]-benzyl}-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-benzamidine;
- 3-{4-[4-(2,6-Dimethyl-piperidin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-hydroxy-benzamidine;
- 25 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-N-methyl-benzamidine;
- {2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl}-acetic acid;
- 30 3-(4-{3-[(Diisopropylamino)-methyl]-benzyl}-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-benzamidine;
- 3-{4-[3-(2,6-Dimethyl-piperidin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

-164-

- 2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-
pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid;
- 3-{3-Oxo-4-[4-(pyridin-2-ylamino)-butyl]-3,4-dihydro-2H-
benzo[1,4]oxazin-2-yl}-benzamidine;
- 5 2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-
pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid
methyl ester;
- 3-[4-(5-Dihexylamino-pentyl)-3-oxo-3,4-dihydro-2H-
benzo[1,4]oxazin-2-yl]-benzamidine;
- 10 3-{4-[4-(Methyl-pyridin-2-yl-amino)-butyl]-3-oxo-3,4-dihydro-
2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-[3-(imino-morpholin-
4-yl-methyl)-phenyl]-4H-benzo[1,4]oxazin-3-one;
- 3-{3-Oxo-4-[4-(pyrimidin-2-ylamino)-butyl]-3,4-dihydro-2H-
benzo[1,4]oxazin-2-yl}-benzamidine;
- 15 3-[4-(4-Cyclohexylamino-butyl)-3-oxo-3,4-dihydro-2H-
benzo[1,4]oxazin-2-yl]-benzamidine;
- 3-{4-[5-(2,5-Dimethyl-pyrrolidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-
2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 20 3-[4-(5-Morpholin-4-yl-pentyl)-3-oxo-3,4-dihydro-2H-
benzo[1,4]oxazin-2-yl]-benzamidine;
- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-2,3-dihydroxy-pentyl]-3-
oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 4-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-
benzo[1,4]oxazin-4-ylmethyl]-N,N-dimethyl-benzamide;
- 25 2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-
pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxylic acid;
- 3-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-
benzo[1,4]oxazin-4-ylmethyl]-N,N-dimethyl-benzamide;
- 30 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pent-2-enyl]-3-oxo-3,4-
dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
- 3-[4-(5-Amino-pentyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-
yl]-benzamidine;

-165-

2-(3-Carbamimidoyl-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxylic acid methyl ester;

5 4-Methoxy-3-[4-(4-methoxy-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-benzonitrile;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pent-3-enyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;

4-[2-(3-Cyano-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-N,N-dimethyl-benzamide;

10 3-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-5-(2,6-dimethyl-piperidin-1-ylmethyl)-benzoic acid;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-4-hydroxy-benzamidine;

15 3-Acetyl-2-(2-methoxy-phenyl)-thiazolidine-4-carboxylic acid 4-cyano-2-{4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-phenyl ester;

3-[2-(3-Carbamimidoyl-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-5-(2,6-dimethyl-piperidin-1-ylmethyl)-N-hydroxy-benzamide;

20 4-(2-Dimethylamino-ethyl)-7-nitro-2-phenyl-4H-benzo[1,4]thiazin-3-one;

4-(2-Diethylamino-ethyl)-7-nitro-2-phenyl-4H-benzo[1,4]thiazin-3-one;

25 2H-1,4-Benzothiazin-3(4H)-one, 4-[2-(dimethylamino)ethyl]-7-nitro-2-phenyl-, monohydrochloride;

2H-1,4-Benzothiazin-3(4H)-one, 4-[2-(diethylamino)ethyl]-7-nitro-2-phenyl-, monohydrochloride;

30 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-methoxy-phenyl)-4H-benzo[1,4]thiazin-3-one;

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-benzonitrile;

-166-

4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-thiobenzamide;

4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-methoxy-phenyl)-4H-benzo[1,4]thiazin-3-one; compound with trifluoro-acetic acid;

5 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-benzonitrile;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-benzamide;

10 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(3-methoxy-phenyl)-2-(4-methoxy-phenyl)-4H-benzo[1,4]thiazin-3-one;

4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-(4-methoxy-phenyl)-1,1-dioxo-1,4-dihydro-2H-1,4-benzo[1,4]thiazin-3-one;

2-(4-Benzyloxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]thiazin-3-one;

15 2-(4-Butoxy-phenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]thiazin-3-one;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-thiobenzamide;

20 4-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-benzamidine;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-N-hydroxy-benzamidine;

3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-benzamidine;

25 3-{4-[5-(2-Hydroxymethyl-pyrrolidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-yl}-benzamidine;

4-Allyl-2,2-diphenyl-4H-benzo[1,4]thiazin-3-one;

4-(2-Diethylamino-ethyl)-7-nitro-2-phenyl-4H-benzo[1,4]thiazin-3-one;

30 2-(3-Diethylamino-propylamino)-4-methyl-2-phenyl-4H-benzo[1,4]thiazin-3-one;

4-(2-Diethylamino-ethyl)-2,2-diphenyl-4H-benzo[1,4]thiazin-3-one;

-167-

- 2-Benzyl-4-(5-piperidin-1-yl-pentyl)-4H-benzo[1,4]oxazin-3-one;
 2-Cyclohexyl-4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-4H-benzo[1,4]thiazin-3-one;
 2H-1,4-Benzothiazin-3(4H)-one, 4-methyl-2,2-diphenyl-;
 4-Ethyl-2-phenyl-2-piperidin-1-yl-4H-benzo[1,4]thiazin-3-one;
 4-Methyl-2-phenyl-2-piperidin-1-yl-4H-benzo[1,4]thiazin-3-one;
 3-{4-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-piperidine-1-carboxamidine;
 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-piperidin-3-yl-4H-benzo[1,4]oxazin-3-one;
 3-Oxo-2-phenyl-2,4-bis-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbonitrile;
 4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-2-pyridin-2-yl-4H-benzo[1,4]oxazin-3-one;
 N-Hydroxy-3-oxo-2-phenyl-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxamidine;
 3-Oxo-2-phenyl-4-(5-piperidin-1-yl-pentyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxamidine;
 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-thiobenzamide;
 3-{4-[5-(Adamantan-1-ylamino)-pentyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl}-benzamidine;
 2-(3-Diethylamino-propylamino)-4-methyl-2-phenyl-4H-benzo[1,4]oxazin-3-one;
 4-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-2-phenyl-2H/-1,4-benzoxazin-3(4H)-one; or
 4-Methyl-2-phenyl-2H/-1,4-benzoxazin-3(4H)-one.

19. A method for the treatment or prophylaxis of thrombotic disorders in a mammal comprising administering to said mammal an effective amount of a compound according to Claim 1.

-168-

20. A method according to Claim 19, wherein said disorder is venous thrombosis.
21. A method according to Claim 19, wherein said disorder is arterial thrombosis.
- 5 22. A method according to Claim 19, wherein said disorder is pulmonary embolism.
23. A method according to Claim 19, wherein said disorder is myocardial infarction.
- 10 24. A method according to Claim 19, wherein said disorder is cerebral infarction.
25. A method according to Claim 19, wherein said disorder is restenosis.
26. A method according to Claim 19, wherein said disorder is cancer.
27. A method according to Claim 19, wherein said disorder is angina.
28. A method according to Claim 19, wherein said disorder is diabetes.
- 15 29. A method according to Claim 19, wherein said disorder is atrial fibrillation.
30. A method according to Claim 19, wherein said disorder is heart failure.
31. A pharmaceutical formulation comprising a compound of claim 1 admixed with a carrier, diluent or excipient.
- 20 32. A pharmaceutical formulation comprising a compound of Claim 2 together with a carrier, diluent or excipient.

-169-

33. A pharmaceutical formulation comprising a compound of Claim 14 together with a carrier, diluent or excipient.
34. A pharmaceutical formulation comprising a compound of Claim 15 together with a carrier, diluent or excipient.
- 5 35. A method for inhibiting serine proteases comprising administering to a mammal an effective amount of serine protease inhibitor of Claim 1.
36. A method according to Claim 35, wherein said serine protease is factor Xa.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 98/26708

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D265/36 C07D279/16 A61K31/535 A61K31/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 116 368 A (SANTEN PHARMA CO LTD) 22 August 1984 cited in the application see pages 33,34,41-48, claims ---	1-6, 18, 31-34
X	EP 0 237 573 A (SANTEN PHARMA CO LTD) 23 September 1987 see claims & US 4 786 635 A cited in the application ---	1-6, 18, 31-34
X	FR 2 332 756 A (SQUIBB & SONS INC) 24 June 1977 see the whole document ---	1-6, 18, 31-34
X	FR 2 111 728 A (SQUIBB & SONS INC) 9 June 1972 see the whole document ---	1-6, 18, 31-34
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 March 1999

Date of mailing of the international search report

23/03/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 98/26708

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 079 223 A (DEUTSCHES HYDRIERWERK) 12 November 1971 see the whole document & DE 20 44 530 A cited in the application ---	1-6, 18, 31-34
X	GB 1 174 626 A (LABORATOIRE ROGER BELLON) 17 December 1969 see the whole document ---	1-6, 18, 31-34
A	WO 96 07648 A (WARNER LAMBERT CO) 14 March 1996 see claims ---	1-36
P,A	WO 98 21186 A (CEPHALON INC) 22 May 1998 see claims ---	1-36
P,A	WO 98 50372 A (SCHERING AG.) 12 November 1998 see claims -----	1-36

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/26708

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-30, 35-36
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19-30, 35-36
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/26708

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0116368	A	22-08-1984	JP 1845004 C	25-05-1994
			JP 59144775 A	18-08-1984
			JP 1815241 C	18-01-1994
			JP 5026785 B	19-04-1993
			JP 59148771 A	25-08-1984
			AT 30421 T	15-11-1987
			AU 570667 B	24-03-1988
			AU 2376784 A	16-08-1984
			CA 1245650 A	29-11-1988
			DE 3466987 A	03-12-1987
			DK 53784 A,B,	08-08-1984
			FI 840482 A,B	08-08-1984
			US 4584300 A	22-04-1986
EP 0237573	A	23-09-1987	WO 8700837 A	12-02-1987
			AT 71622 T	15-02-1992
			AU 587057 B	03-08-1989
			AU 6137186 A	05-03-1987
			DE 3683483 A	27-02-1992
			DK 158087 A	27-03-1987
			FI 871322 A,B	26-03-1987
			WO 8700838 A	12-02-1987
			JP 1861239 C	08-08-1994
			JP 62123181 A	04-06-1987
			US 4786635 A	22-11-1988
FR 2332756	A	24-06-1977	DE 2653819 A	02-06-1977
			JP 52065280 A	30-05-1977
			US 4107167 A	15-08-1978
FR 2111728	A	09-06-1972	CA 995669 A	24-08-1976
			CH 539633 A	14-09-1973
			DE 2152282 A	27-04-1972
			GB 1374283 A	20-11-1974
			US 3725403 A	03-04-1973
FR 2079223	A	12-11-1971	CH 555356 A	31-10-1974
			DE 2044530 A	19-08-1971
GB 1174626	A	17-12-1969	FR 7614 M	19-01-1970
			FR 1561854 A	28-03-1969
WO 9607648	A	14-03-1996	US 5652237 A	29-07-1997
			AU 3496295 A	27-03-1997
WO 9821186	A	22-05-1998	AU 7179598 A	03-06-1998
WO 9850372	A	12-11-1998	AU 8330898 A	27-11-1998

THIS PAGE BLANK (USPTO)